AUG 18 1920

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

Vol. XXXI—No. 354] BALTIMORE, AUGUST, 1920 [Price, 50 Cents

CONTENTS

	PAGE
Capillary Poisons and Shock. (Illustrated.) By H. H. Dale	257
A Study of the Cardiovascular Reaction to Epinephrin. Epinephrin Sensitiveness in Patients with Hypertension. (Illustrated.) By Paul W. Clough	266
A Clinical Study of Thirty-Nine Cases of Combined Thoracic and Abdominal Wounds. By George J. Heuer	273
The Natural History of Typhoid Fever in Baltimore, 1851-1919. By William Travis Howard, Jr.	276
A Study of the Invalid Reaction. By Esther Loring Richards	286

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917. Authorized on July 3, 1918.

CAPILLARY POISONS AND SHOCK[1]

By H. H. Dale

(From the Lister Institute of Preventive Medicine, London, England)

May I begin by expressing my very deep sense of the honor which has been done to me in the invitation to deliver the Herter lectures in this world famous university? I can conceive for no worker in science a greater honor, or a keener pleasure, than that afforded by such a request to come from afar and talk about his own work, his own ideas, hopes and failures, with those from whom he has hitherto drawn inspiration and encouragement, whose scientific fellowship he has hitherto been able to enjoy, mainly through the printed, or, at best, the written word.

For myself, I have found in this invitation, not only pleasure and gratification, though these in abundance, but a measure of embarrassment. In the case of any one of the distinguished men who have preceded me in this lectureship, it would not be difficult to point to one or more fields of investigation in which his work had conspicuously aided progress, with which, in the terms attached to Dr. and Mrs. Herter's noble gift, he had himself been identified. Any one in touch with the progress of medical science would know what the Selection Committee had in mind, what they expected from the lecturer, when the invitation was given. Looking back over the past 15 years, I have been bound to admit that I can trace in my own case no consistent devotion to any line of work. I seem to have been drawn into a number of apparently disconnected investigations by curiosity, the accident of routine, above all, by the happiness of association with a small company of brilliant and enthusiastic colleagues. The only real link of connection seems to have been at the common starting point of these joint expeditions, which was curiously remote from most of our ultimate destinations.

The starting point has an interest more personal than scientific, and I allow myself the egotism of allusion to it, partly to provide myself now, as then, with a point of departure, but more especially to enable me to pay a passing tribute to the broadminded policy which enabled my colleagues and myself, in circumstances where many would not expect such freedom, for years to follow the lead of purely scientific interest, unhampered by considerations of immediate practical outcome. Dr. Barger and I were asked in 1904 to undertake an investigation of the chemistry and pharmacology of ergot. We determined to take, one by one, any characteristic forms of physiological activity which I could detect in the substance and its extracts, and to use each in turn as a guide to the chemical isolation and identification of the substance producing it. We believed the problem to be a difficult one, but it proved to have a complexity and an interest altogether beyond our expectation. It was our great good fortune to find in ergot a veritable treasure house of substances, presenting, in intense degrees, the most varied forms of pharmacological activity and in the study of these, my colleagues and

[1] Lecture I of the Herter Series delivered before The Johns Hopkins University, November 13, 1919.

I wandered far from the immediate problem of the therapeutic action of ergot, into an investigation of the epinephrine type of action and its relation to the effects on true sympathetic nerves of the muscarine type of action and its relation to the effects on other nerves of the autonomic system; and into a study of the effects of substances producing a shock-like depression of the circulation, similar to that encountered in a large class of pathological conditions. It is to an analysis of this last-mentioned, curious and, as I believe, widely significant type of action, that I desire to ask attention to-day. In a second lecture I hope to deal with a special example of it in the so-called anaphylactic shock. In a third lecture I shall endeavor, by a transition which, as I hope to convince you, is less forced and abrupt than might appear, to pass from the anaphylactic phenomena to a more general consideration of the connection between chemical structure and physiological action, as illustrated by the action of certain groups of substances related to the other active constituents of ergot. For the present I invite your attention to a shock-like effect, on the circulation and other vital activities.

We had long known that ergot extracts exhibited a direct and intense stimulant action on plain muscle, and, in particular, on the plain muscle of the uterus. None of the principles which we had hitherto identified would account satisfactorily for this action, which, on the face of it, seemed to be more directly related to the therapeutic use of the drug than the other types of activity which we had described. At length, after many methods had been tried in vain, Barger succeeded, by using Kutscher's method of separating such substances as the organic bases in meat extract, in isolating a base from ergot which produced this action with extraordinary intensity. One part of this base in 100 millions of solution had still a pronounced effect on the tone of uterine muscle. It proved to be one of the series of amines formed by decarboxylation of amino-acids. In this instance the parent amino-acid was histidine, and the identification of the base was greatly facilitated by the fact that Ackermann, almost simultaneously, produced it from histidine by the action of bacteria. General usage has conveniently and appropriately named it "histamine." The interest of this substance, however, was by no means limited to its occurrence in and contribution to the activity of ergot. The significance of its action began to appear only when its physiological effects came to be more closely analyzed, and the investigation has led us far, indeed, from our original objective. When Laidlaw and I began to examine the action of this substance more closely, we soon recognized that it produced, in relatively minute dosage, a type of effect long familiar, though incompletely understood. This type of action had hitherto been identified with the action of certain products of the partial cleavage of proteins, such as the familiar Witte's peptone, certain protamines and histones, and the products of gentle alkaline hydrolysis obtained by Vaughan and his colleagues. It was, perhaps, of special interest that an action of this general type had been demonstrated with extracts from a large number of different organs of the animal body. Popielski had postulated the presence in all such extracts and hydrolytic products of a hypothetical principle, "vasodilatin." Just before we began to examine the action of histamine, this type of action had acquired a new and absorbing interest from the fact that it was found to be faithfully reproduced in, to constitute, indeed, the complex of symptoms known as the anaphylactic shock, even to the details of variation which that phenomenon showed in the different species. So that, within a single year, this same complex of symptoms, hitherto known as the effect of products of protein digestion and of organ extracts, was found to be reproduced in the reaction of a specifically sensitized animal to a normally inert protein, and in the action of a pure base, obtainable by a relatively simple change from one of the amino-acids out of which the protein molecule is built.

I need hardly indicate the temptation which was presented to any one coming upon these facts for the first time. I have mentioned Popielski's view that the various organ extracts and crude products of digestion owed their common type of activity to the presence, in varying proportions, of a single active substance. The idea that the anaphylactic phenomena were due to the production in the circulation of a substance of this type, by the action of a specific ferment, was already in the air. The suggestion lay near at hand that the long-sought active substance was "histamine," and that the production of the latter in the system was the cause of the anaphylactic shock. The temptation to make such a suggestion was even accentuated, when Barger and I were able to show that in one particular organ extract, that from the intestinal mucosa, histamine was actually present. The suggestion, however, was not made by us, though others were not slow to make it for us, and even to attribute to us the view that the anaphylactic shock was due to the liberation of histamine. The presence of histamine in extracts of other tissues than the intestinal mucous membrane, remained for us a highly speculative possibility; as for the anaphylactic shock, my own observations soon led me to a conception of this phenomenon in which histamine played no direct part, and which I shall endeavor to explain to you in my next lecture.

It may be that the event will prove us to have been too cautious. You will be familiar with the highly suggestive experiments recently carried out here by your own distinguished Professor of Pharmacology, Dr. Abel, in association with Dr. Kubota. These experiments have again placed in the center of interest for all workers in this field the possibility that histamine itself, or some compound or derivative of histamine, may be the active constituent in the different impure cleavage-products and organ extracts which have this type of action. Dr. Abel would not expect or value from me the empty compliment of an assumption that he has completed a proof towards which his work has made a beginning brilliant with promise. If he succeeds in proving that histamine itself, or some recognizable derivative, is split off from protein in hydrolysis, or from tissues in death or early autolysis, he will have built a firm structure where my colleagues

and I have merely sketched a vague outline and [illegible] will rejoice more sincerely than we.

Meanwhile, he will understand my desire to leave this chemical aspect of the question open, and to direct your attention to the nature and significance of the type of physiological action, which the discovery of the action of histamine enabled us to investigate.

If our study of this symptom-complex, produced by histamine or any of these protein derivatives, had been carried out with impure extracts or complex products of digestion, we should probably have been led to assume that more than one active principle was at work, especially in producing the effects on the circulation; for the action on certain species might easily suggest a conflict of opponent actions. The discovery of all these various and, in some ways, apparently conflicting effects in the action of the one pure substance, histamine, cleared our minds of any suggestion of a multiplicity of principles, but left us faced with a paradox, which for years has held our interest, and until quite recently has baffled all attempts at explanation. It can be stated in a few words. Histamine, and the group of protein derivatives having a generally similar type of action, have a powerful stimulant effect on the tone of all plain muscle. Not merely the uterine muscle, the action on which first came to light, but the muscular coats of the bowel, the bronchi and of the arteries are stimulated to strong tonus. If the blood vessels of any organ, from any animal, are perfused artificially with blood or Ringer's solution, histamine, added in any effective dose to the perfusion fluid, causes pronounced contraction of the arteries, as shown by retardation of the flow of fluid and shrinkage of the organ. The same stimulation of tone by histamine is observed in a strip of arterial wall suspended in Ringer's solution, as several observers using arteries from different species and different parts of the system, have shown here in Professor Abel's laboratory. Now in some species, such as the rabbit, this effect is visibly reproduced *in vivo*, a small dose of histamine, under conditions eliminating complication from effects on the pulmonary circulation, causing a simple rise of arterial blood-pressure by vasoconstriction; in other species, however—in the carnivora, in the monkey, probably in man—the effect of a small dose of histamine, injected into the living circulation, appeared to be the exact opposite of this. A fall of arterial blood-pressure was the invariable result, and the most careful analysis of this, by means of the plethysmograph and the cardiometer, as well as by simple inspection of exposed organs, left no escape from the conclusion that this fall of blood-pressure was due to vasodilatation, to a general weakening of the peripheral resistance, and not to diminished output from the heart, or to obstruction of the blood-flow through the liver, as Mautner and Pick suggested. In these species, therefore, we had the most complete apparent contrast between a vasoconstrictor effect of histamine, increasing the resistance to the blood-flow through an artificially perfused organ, and a vasodilator effect of histamine, diminishing the resistance to the flow in organs perfused by the natural circulation.

In what way did the conditions of natural differ from those of artificial perfusion? An obvious possibility was the existence of some nervous mechanism, which did not survive under the artificial conditions. I need not trouble you with the details of the investigations, by Laidlaw and myself, in which such possible nervous mechanisms, in the spinal cord, in the sympathetic ganglia, in the peripheral nerve-endings were, one by one, eliminated. I need only refer to the last stage of this elimination, which occurred in a recent renewal of the attack on this problem, in which I had the great privilege of coöperation with Professor Richards of Philadelphia. Richards and I found that, when all the nerves to a limb, or to a loop of the bowel, had been cut and allowed to degenerate completely, the dilating effect of histamine on the vessels, thus completely denervated, was not abolished, but, on the contrary, was habitually much intensified.

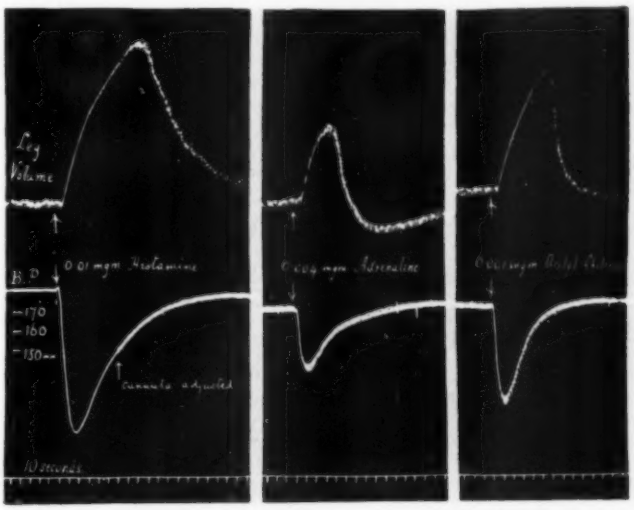

FIG. 1.—Volume of leg completely denervated by degeneration; blood-pressure. Intravenous injections as indicated. (Dale and Richards, Journ. of Physiol., LII, p. 120, Fig. 4.)

On the other hand, if such a denervated limb was artificially perfused with blood, the addition of histamine to the blood caused vasoconstriction of at least normal intensity. So that both the vasoconstrictor effect on the artificially perfused organ and the vasodilator effect on the naturally perfused organ were purely peripheral effects, independent of the integrity of the nerve supply. The paradox was more complete, more sharply defined than ever. We had no clue here to the missing factor in the artificial perfusion. What we believe to be the correct clue to the meaning of this paradox was first obtained from experiments which Laidlaw and I had already made on the effects of comparatively large, seriously poisonous doses of histamine. I shall have more to say concerning these later, but may mention now that they seemed, in large measure, to be due to a poisoning of the capillary endothelium. The suggestion that the evanescent, vasodilator action of small doses was also an action on the capillaries, that it represented not a relaxation of arterial tone,

but of an intrinsic tone of the capillary walls, began to take form in our minds. I believe Laidlaw first had the insight, or the hardihood, to give it expression. To consider it was to run counter to the accepted physiological teaching; but the paradox still awaited explanation, and we seemed to have exhausted other possibilities.

Richards and I attempted to put it to the test in two ways. In the first place, we endeavored to determine the conditions in the living animal which favored or accentuated the vasodilator effect of small doses of histamine. We studied the condition of the circulation in the hind limb of the cat, at different intervals after section of all the nerves, and we found what we regarded as evidence of independent variation of the

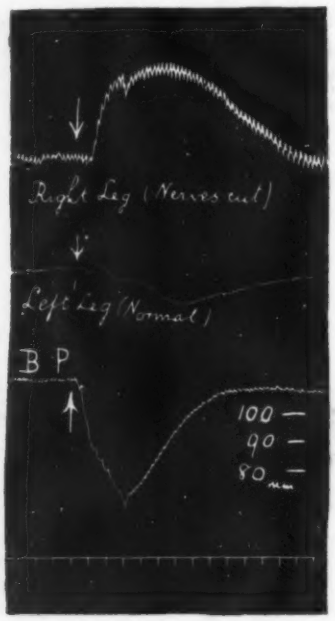

Fig. 2 (I).—Effect of 0.01 mgm. histamine. Volumes of leg with nerves freshly cut and of normal leg; blood-pressure. (Dale and Richards, Journ. of Physiol., LII, p. 125, Fig. 7.)

tone of the arteries and the capillaries. There was one condition, in particular, appearing very soon after the nerves had been divided, which we could only interpret as due to dilatation of the arterioles and constriction of the capillaries. The volume-pulse of the limb, as registered by a plethysmograph, was greatly exaggerated, showing that the arteries were widely dilated; the skin in an unpigmented animal, best seen on the hairless pads of the foot, was pale, showing that the capillaries were constricted; and this combination of arterial relaxation and capillary tone produced a rapid circulation through the skin, so that the surface was warm. In the normal limb, on the other hand, especially in cold weather, the converse condition was observed; the volume-pulse was small, and the pads of the feet were red, but cold to the touch, which we regarded as indicating that a small stream of blood, thro[illegible]onstricted arterioles, was spread out to circulate slowly through a relaxed network of capillaries. When this contrast of warm pallor and cold congestion was well marked between the two limbs, there was always a pronounced contrast between the dilating action of histamine on the two. The pale and warm denervated limb, in which the capillary tone was good, always showed a well-marked expansion; the normal limb, with cold, red pads, showed a relatively very small expansion, or even an actual shrinkage with the fall of blood-pressure caused by histamine. In other words, it appeared to us that, irrespective of the condition of the arteries if the capillary tone was high, giving scope for capillary relaxation, the dilator effect of histamine was accentuated; but that, if the capillaries were already relaxed so that little further effect in that direction was possible, the dilator effect of histamine was weak or absent. It would

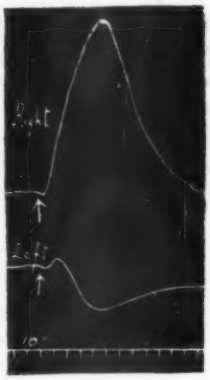

Fig. 2 (II).—Right sciatic and anterior crural nerves cut 5 days previously. Left leg normal. Effect of 0.01 mgm. histamine. (Dale and Richards, Jour. of Physiol., LII, p. 132, Fig. 12.)

take too long to describe the corroborative evidence obtained by studying the effects on vessels subjected to temporary anæmia and cold. I can only say that it all seemed to point in the same direction, namely, to the conclusion that the vasodilator effect of histamine was an effect on the capillaries and not on the arteries. Then, in the second place, we made experiments on the conditions which would enable histamine to produce this vasodilator effect even in the perfused organ in which it had never hitherto been observed. We found the condition in a combination of two factors. (1) The supply to the tissues of abundant oxygen must be ensured by the presence of red corpuscles in the perfusion fluid; and (2) a small proportion of epinephrine must also be present. Neither alone was effective. The organ might be well oxygenated by using a suspension of red corpuscles or hirudinised blood; or epinephrine might be added to gum-saline solution so as to produce a high arterial resistance to perfusion; but histamine still increased the resistance to perfusion, retarded the venous outflow and caused shrinkage of the organ. Only if both

red corpuscles and epinephrine were added, and the airways, did histamine produce in the perfused organ its normal effect, as produced by small doses in the living body—weakening of resistance, accelerated venous outflow and expansion of the organ-volume (Figs. 3, 4, 5 and 6). Note that in Fig. 3, when epinephrine alone is added, and in Fig. 5, when blood without epinephrine is used, histamine causes only vasoconstriction. Only in Figs. 4[b] and 6, when both red cells and

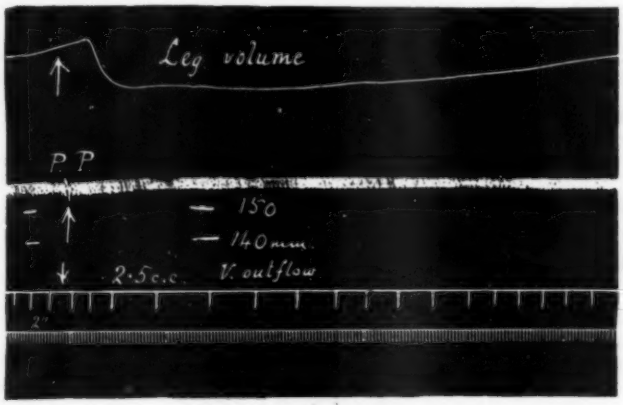

FIG. 3.—Perfusion of leg with gum-Ringer and adrenaline (1 in 2½ millions). Effect of 0.03 mgm. histamine. (Dale and Richards, Journ. of Physiol., LII, p. 150, Fig. 16.)

epinephrine are present, is the vasodilation effect to be seen. In these and other tracings acetylcholine is used, by way of constrast, as a typical *arterial* dilator, producing its vasodilator action under all conditions. This seemed to us again to point to the production of the vasodilator effect of histamine

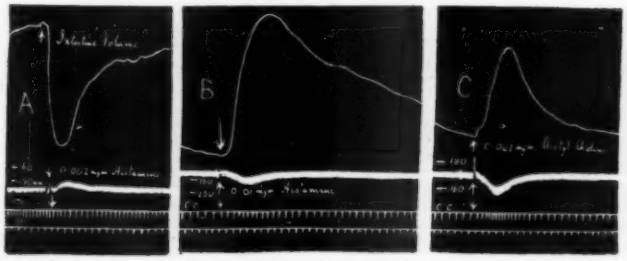

FIG. 4.—Perfusion of intestinal loop with hirudinised blood. Oncometer, perfusion pressure, and venous outflow. A before, B and C after addition of 1 part of adrenaline to 1 million of perfusing blood. (Dale and Richards, Journ. of Physiol., LII, p. 150, Fig. 17.)

by an action on vessels far more sensitive to an adequate oxygen supply than the arterioles. With arterial dilators, such as acetylcholine or the nitrites, there is no difficulty in demonstrating the vasodilator effect in an organ perfused with simple saline solution. The relation between the increase of organ-volume produced by histamine and its effects on the resistance and venous outflow seemed also to indicate its action on vessels more peripheral than those affected by an arterial dilator. It will be seen in Fig. 4 that that increase of organ-volume produced by histamine is very large in relation to the acceleration of venous outflow. Finally we were able to put this idea to the test of an anatomical separation. We perfused the arteries in a triangular segment of mesentery, cut-

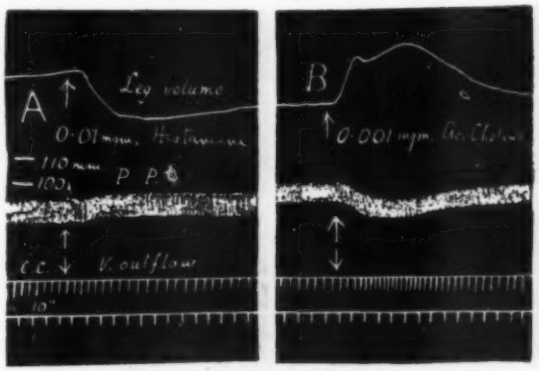

FIG. 5.—Completely denervated leg perfused with hirudinised blood (no adrenaline added). (Dale and Richards, Journ. of Physiol., LII, p. 151, Fig. 18.)

ting away the corresponding loop of intestine as close as possible to its mesenteric attachment and measuring the outflow from the open ends of the fine arterial branches thus cut across. Even when blood and epinephrine were perfused, histamine invariably caused further constriction, shown by retarded

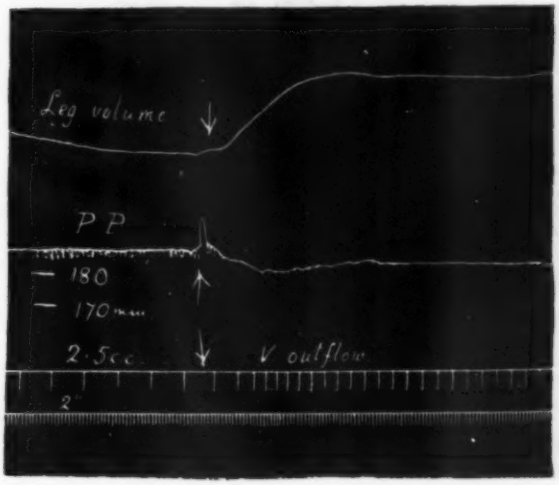

FIG. 6.—Perfusion of normal leg with hirudinised blood to which 1 part of adrenaline in 10 millions has been added. Effect of 0.1 mgm. histamine. (Dale and Richards, Journ. of Physiol., LII, p. 151, Fig. 19.)

outflow, while acetylcholine regularly caused relaxation (Fig. 7). Yet, under these same conditions the flow through the loop of bowel, containing the capillary distribution of these arterioles, had always been accelerated and its volume increased, by similar doses of histamine. We arrived then at a conception of the action of histamine on the blood vessels which involved a dual mechanism; an increase of the tone of the arterial plain muscle, and a relaxation of the tone of the

capillaries. Either effect might be predominant according to the conditions of the test. When the natural tone of the capillaries was good, the dilator effect on the capillaries was the conspicuous and effective factor, especially when the dose was small; for the sensitiveness of the capillaries to this action is extraordinarily high. As little as the 100 millionth part of a milligram has been observed to give a definite effect. On the other hand, if the capillaries were already relaxed, the effect on the arteries would predominate, and we should obtain a purely vasoconstrictor effect, as in the ordinary perfusion experiment, if either red corpuscles or epinephrine were absent.

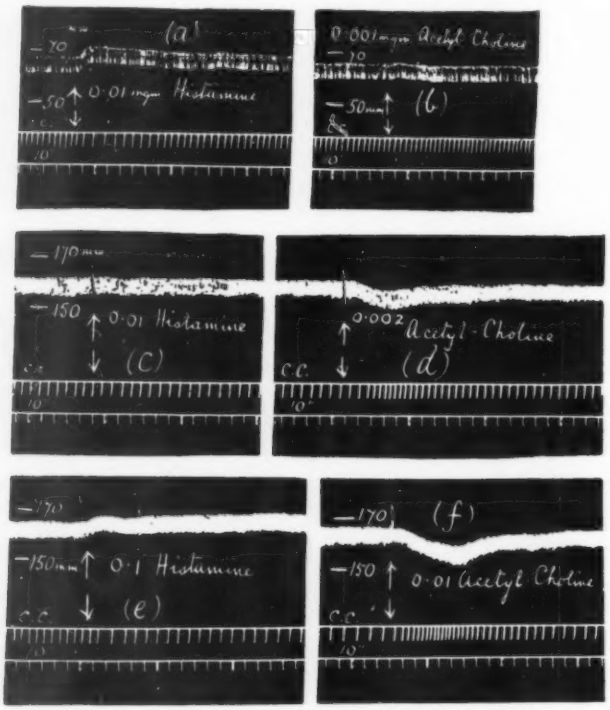

FIG. 7.—Perfusion of branches of superior mesenteric artery with hirudinised blood. (a) and (b) before, (c), (d), (e) and (f) after adding 1 part of adrenaline to 1 million of blood. Perfusion pressure and outflow from cut arterioles. (Dale and Richards, Journ. of Physiol., LII, p. 157, Fig. 20.)

I hope I have succeeded in making clear the kind of evidence we obtained. It is difficult, with the necessary brevity, to give an impression of the effect of the different threads of argument converging to one conclusion. Yet the point is one on which I should like to carry conviction, for so much springs directly from it in the way of suggestion as to the physiological control of the circulation. The idea of an independent contractility of the capillaries is no new one. Since Stricker first credited them with this function in 1865, there have been numerous observations confirming the power of these vessels to vary their lumen from complete occlusion to wide patency, independently of the arterial pressure. Some, like Stricker himself, have attributed these changes to a varying turgescence of the capillary wall rather than to active contraction. Others, such as Rouget, Mayer and Steinach and Kahn, have described the capillaries as possessing a delicate coat of actively contractile cells, surrounding the endothelial wall, and comparable in function to the plain muscle coat of the arterioles. Roy and Graham Brown, while not committing themselves as to the exact nature of the process, were convinced that the contractility of the capillaries was not an occasional, abnormal function, but was always in action, so that these vessels had a tone of their own, capable of intensification or relaxation. While the existence of such a function was generally admitted, however, it was not until recently credited with more than a local and exceptional influence on the circulation. Langley thought that the shifting incidence of the state of contraction of capillaries might ensure that each section of a tissue received a supply of blood, under conditions of pressure too low to maintain a simultaneous circulation through the whole. Cotton, Slade and Lewis attributed some of the phenomena of dermography, and the local pallor caused by epinephrine in a limb in which the circulation has been stopped, to action on capillary tone. But I think it may fairly be stated that, in the prevalent conception of the manner in which the circulation is maintained, of the nature of the peripheral resistance upholding the general arterial pressure and changing the distribution of the blood-flow in accordance with the needs of the tissues, the independent tone of the capillaries has played no part of any significance. It is believed that the effective resistance to blood-flow is in the arterioles, and that when the blood leaves these for the capillaries, it enters a region where the resistance is relatively trivial. Now if calculations be based on the sectional areas of the whole available capillary network, such a conclusion is inevitable, for the path then available for the blood is so wide, the rate of its flow correspondingly so slow, that the frictional resistance must be negligible as compared with that in the arterioles. A study of the rates of flow in a tissue such as the web of a frog's foot leads to a similar conclusion. On the other hand, if our results with histamine have been rightly interpreted, they indicate that, in the body as a whole, the capillaries in their normal state of tonus, contribute an effective part of the resistance to the blood-flow, so that a simultaneous weakening of the capillary tone over a large area may cause a fall of arterial pressure, by diminution of the peripheral resistance, very similar to that caused by arterial relaxation. This is a conclusion which those who have long been engaged in investigating and teaching the physiology of the circulation find very difficult to accept. On the ordinary conception of the capillary network, as depending for its state of fullness or depletion entirely on the tone of the arteries and the pressure in the veins, it would clearly be impossible. Indeed, I think, and shall presently show reason for believing, that when all the capillary channels are open and simultaneously available for the passage of blood, the capacity of the capillary network is such that a large part of the blood pours into it and stagnates as in a morass. Our view of the capillaries, under normal conditions, as opposing an effective resistance to the blood flow, necessarily entails the belief that

only a very small proportion of the available capillary paths, in the tissues as a whole, are at any one moment normally serving as a channel for the transmission of blood, the rest being closed by intrinsic tonus.

We should suppose that the incidence of this occlusion is constantly shifting, some paths opening as others close, but the average total path remaining fairly constant in the resting tissue, and remaining so small as to contribute effectively to the peripheral resistance. Under the influence of a small dose of histamine or of other substances acting in a similar manner, the channels already open would become wider, possibly to some extent channels completely closed would open, the resistance to blood flow would be diminished, and an effect on the arterial pressure very similar to that of an arterial dilatation would be produced.

We had already reached this conception by indirect argument from this action of histamine, when a paper appeared by Krogh, who had devised new and beautiful methods for directly observing the state of the capillaries, not merely in transparent membranes, as previous observers had done, but in the really effective tissues, the functional master tissues, such as the skeletal muscle, of which the large mass of the body is formed. Krogh was able to show that in the resting muscle of the frog or the mammal, the portion of the available capillary network actually in use is surprisingly small. On the other hand, in the active muscle a great number of additional channels were opened up and the paths became not only more numerous, but wider; so that, in one determination, the volume of blood in the active muscles of a guinea-pig was 275 times as great as in the muscle at rest, while the maximum blood content of the muscle, with all the capillary channels dilated, was no less than 750 times the minimum. Krogh, who investigated this mechanism from the point of view of the oxygen supply to the tissues, showed that only by such active variation in the lumina of the capillaries could the blood supply be adapted to the fluctuating needs of the tissue for oxygen.

From an entirely different point of view, therefore, Krogh reached a conception of the capillary circulation which fundamentally accorded with ours. It seems to me clear that, apart from the coarse adjustment of the blood supply to whole organs or areas of tissue, effected by the variations in arterial tone under the influence of the nerves or of epinephrine, we have to take account also of a fine adjustment of the blood supply to the varying needs of separate small areas of tissue, or even of individual cells, carried out by the changing tone of the capillaries. The question arises as to the mechanism by which this fine adjustment is controlled. Steinach and Kahn described a contraction of the capillaries in the frog's nictitating membrane when the sympathetic chain was stimulated, and Krogh has recently described a spread of capillary dilatation from a punctiform stimulus, apparently due to an axon reflex through the branched termination of sensory fibres. On the other hand, the body supplies abundant examples of a joint nervous and chemical control; and, if a momentary lapse into teleology be permissible, it may be pointed out that an adjustment of the capillary flow to the local needs of the tissue would be most appropriately effected by the local action of the metabolic products of activity. Such a conception of the capillary dilatation which follows a temporary anæmia was put forward by Roy and Graham Brown, who suggested that possibly even the effect of local irritation might have a similar origin. Barcroft has attributed the vasodilatation accompanying activity in the salivary gland to the action of metabolic products of the activity of the secreting cells. He was speaking of an arterial dilatation, which is the only factor in the increased blood supply that has hitherto received adequate recognition. I find difficulty in supposing that metabolic products, which enter the blood only after it has passed from the arteries, could reach the arterial muscle in sufficient concentration to produce this effect. There is no such difficulty in the conception of an action of this nature, by metabolic products, on the tone of capillaries, with their intimate relation to the active cells of the organ. If it could be supposed that substances, having the type of action that we have considered in the case of histamine, are formed in the tissues, and that their production is accelerated by functional activity, by any influence which renders the existing oxygen supply inadequate for the metabolic need, we should have a mechanism by which not only each organ, but each small part, or even each individual cell, could constantly effect a nice adjustment of the blood-flow to its need for oxygen, and for the removal of harmful waste by the cleansing stream of the circulation. At present such a conception is almost entirely speculative. There is practically no evidence for the production of substances acting like histamine during functional activity of the tissues. It is true, and possibly significant, that substances of this type can be extracted from most of the tissues, even when taken straight from the living body; so that not only by *post-mortem* change, but, at the latest, in the very act of death, such substances are liberated from the cells. To suppose that they are formed as the result of injury not involving death of the cells, or during normal functional activity, may seem a short step, but it is one of such importance that it cannot be safely taken without the support of direct experimental evidence. All that is definitely known of functional activity, such as muscular contraction or glandular secretion, is that it is attended by an increased consumption of oxygen and an increased production of carbon dioxide. Various observers have shown that slight increase of acidity, such as an addition of carbon dioxide to the blood, is attended by vascular relaxation, though whether of arterial or capillary tone has not yet been made clear. On the other hand, we have as yet no real experimental warrant for connecting increased tissue activity with immediate increase of protein breakdown, such as the production of histamine-like substances would seem to entail. It *may* take place, but its occurrence would be difficult to demonstrate, for the quantities needed to cause pronounced capillary dilatation would be so minute as probably to escape detection by the chemical methods available.

I must pass now from the consideration of the evanescent effect of very small doses of histamine to that of the more lasting effects of relatively much larger, though still absolutely small, doses of this powerful substance. We pass, in other words, from the physiological to the pathological signifi-

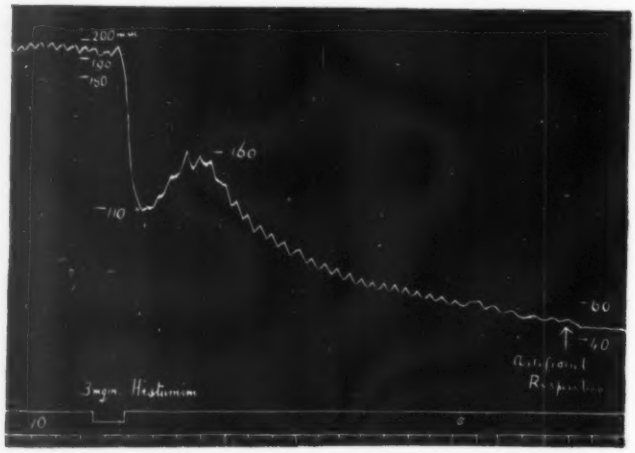

FIG. 8.—Cat. 2.350 kilo. (Dale and Laidlaw, Journ. of Physiol., LII, p. 358, Fig. 1.)

cance of this type of action. From the conception of the dual action which I have already put before you, we might predict the results on the circulation of larger does of histamine, producing the same type of action in a more intense and persistent form. We should expect, in the first place, that the stimulant effects on arterial plain muscle would come more

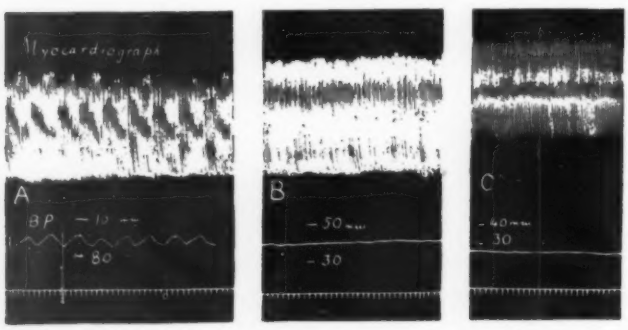

FIG. 9.—Cat. 2.6 kilo. A normal, B 6 minutes, C 18 minutes after injection of 5 mgm. of histamine. (Dale and Laidlaw, Journ. of Physiol., p. 363, Fig. 9.)

into prominence, and, in the second place, that the general and long persistent dilatation of all the capillaries would lead to an accumulation of a large part of the blood in the peripheral reservoir thus opened for its reception. The arterial constriction would make this process slower, but, by more effectively cutting off the driving effect of the heart from the blood stagnating in the lax capillaries, would render it eventually more complete. This anticipation is exactly fulfilled. There is no immediate vasodilator fall such as follows the injection of a minute dose. On the contrary, in the cat under ether there are preliminary phases of the effect which we were able to associate with constriction, first of the pulmonary and then of the systemic arteries. Then followed the main effect of a relatively slow fall of pressure, with a disproportionately rapid decline in the output from the heart (Fig. 8).

This decline of the output from the ventricles is not the result of weakening of the muscular contractions of the heart. These, indeed, are, surprisingly, as powerful as before the drug is given (Fig. 9). Inspection of the heart and great vessels reveals the cause of the condition; the heart and the arteries are almost empty and the great veins are only partly filled. Transparent tissues show a dusky flush of capillary congestion and a network of venules filled with dark blood. The circulation is failing, because the blood is not returning in sufficient volume to the heart to fill its chambers during diastole to more than a small fraction of their capacity. In some way the volume of blood in effective currency has been greatly reduced. One factor in this reduction becomes obvious when the corpuscular content of the blood is examined. In five minutes or so, after administration of 1 or 2 milligrams of histamine per kilogram, the proportion of red corpuscles and the corresponding hæmoglobin value of the arterial blood are raised to a striking degree, often up to 50 per cent or more above the initial values. This is due to actual leakage of plasma from the vessels into the tissues, and a simple calculation shows that half or more of the original plasma may thus have been lost to the circulation in a few minutes. This, in itself, entails a material diminution of the absolute volume of fluid in the vessels. It is not enough, however, to account for the extreme deficiency of blood in circulation. Moreover, if the dose is slowly infused instead of being rapidly injected, an almost equally severe collapse of the circulation from defect of blood in currency, is produced with relatively small loss of plasma as indicated by the corpuscular content. Direct determination by the "vital red" method shows that the same decrease in the volume of effectively circulating blood has, nevertheless, occurred.

Laidlaw and I arrived at the conclusion that the real cause of the oligæmia was a general and simultaneous loss of their normal tone by all the capillaries in the body, so that the blood percolated into the lax network of channels as into a sponge. There was doubt at the time as to the possibility of the capillaries furnishing accommodation for so large a fraction of the blood as to bring about this peripheral stagnation and deplete so seriously the heart and great vessels. Any need for hesitation on this ground, however, has been sufficiently removed by Krogh's determinations, showing that in skeletal muscle at least, the capillaries when fully relaxed can accommodate 750 times the volume which they contain in the resting organ. If we can imagine any such multiplication of the capillary capacity as taking place throughout the body, I think there is no need to look further for the cause of the "oligæmia."

In interpreting these effects, on the circulation of the anæsthetized cat, as due to general loss of the normal tone of the

capillaries, associated with a greater or less development of an abnormal permeability of their walls to the blood plasma, we were not concerned with a mere pharmacological curiosity. No one with even a slight knowledge of the literature dealing with the experimental production of traumatic shock, embodying the observations largely made by your countrymen, could fail to be struck by the similarity of the condition which we were studying with that described as constituting circulatory shock, especially by Yandell Henderson, Mann and others. It was impossible to miss the suggestion that, in at least some of the conditions described as shock and especially in those involving massive injury to the soft tissues, a toxæmic factor might play a prominent part. One of the difficulties in the past had been to bring the experimental work on shock into proper relation with clinical observation, but the experience of surgeons in the late war provided opportunities for comparison in tragic abundance. There was a condition which a group of our military surgeons, with whom at the time was serving Professor Cannon of Harvard, came to recognize as "secondary shock"—a condition slowly developing some hours after extensive injury. We whose work kept us in England, formed a small Shock Committee, and by constant communication with the workers in France we came to realize with increasing clearness that the central feature of the secondary shock was the oligæmia which Henderson and Mann had recognized in their experimental work, and which we had found to be reproduced so faithfully in the effects of larger doses of histamine. The blood was concentrated, the corpuscular content of the capillary blood being notably greater than that of the venous blood. The effective volume of the blood in circulation was greatly reduced; Dr. Keith was able eventually to demonstrate this directly by the use of his "vital red" method. The condition was, with rare exceptions, complicated by hæmorrhage; but, making full allowance for this and for loss of plasma into the tissues, the workers in France were convinced, as we had been, that there was a further loss by peripheral stagnation of blood. Professor Cannon's analysis of the condition, as he studied it in a British Casualty Clearing Station, showed a remarkable concordance with our description of the effects of histamine. Meanwhile, experiments carried out on behalf of your American Shock Committee by Professor Erlanger and his colleagues, with which we were kept in close touch by the kindness of Professor Howell, were leading them to a very similar conception.

It is, perhaps, hardly necessary for me to say that the members of our Shock Committee were making no claim or any attempt to interpret on these lines all the conditions, which have been classed as shock, or even as traumatic or surgical shock. We were simply impressed by the stray suggestion of a toxæmic factor as of central importance in the condition which the war surgeons called "secondary shock." Evidence of a more direct nature was not long wanting. Cannon and Bayliss in England produced the shocklike condition in anæsthetized animals by massive trauma of the muscles of a limb, and showed that severance of all nervous connection did not affect the onset of the shock, while occlusion of the blood vessels prevented it. Quénu and Delbet in France had independently reached a similar view as to the importance in the genesis of shock of the absorption of autolytic products from injured tissues. They, as also McNee and Cannon, demonstrated the protective effect of occluding the blood vessels of the injured limb by pressure and had occasion to record the subsequent onset of shock when the blood was readmitted to the injured tissue. All this evidence emphasizes the probability that a central factor in the secondary wound-shock was the absorption from injured autolysing tissues, and especially from injured muscle, of substances producing the same depressant effect on capillary tone, the same morbid permeability of the capillary walls, as that which we have been considering in the action of histamine. The analogy is made closer by the discovery that hæmorrhage, as well as anæsthesia with ether or chloroform, enormously weaken the resistance to histamine, with which the healthy, unanæsthetized animal can deal in relatively very large doses.

It seems likely, therefore, that more than an accidental and superficial resemblance was involved in the similarity, recognized as long ago as the 1870's, between certain states of traumatic shock and the collapse resulting from a rapidly generalized infection. We arrive at the conception of a group of toxæmias, some of bacterial, some of traumatic origin, due to toxic substances having that same general action on the capillary circulation which we have been considering in the case of histamine. Whatever further chemical investigation may reveal as to the nature of such substances and their relation to histamine, I think there can be little doubt that this conception of the capillaries as an actively contractile part of the vascular system, having an intrinsic tone which can be modified either by nervous or chemical influences, is destined in the future to play a part of increasing importance in conceptions of the mechanism by which the blood supply to the tissues is regulated under normal physiological conditions and of the disturbances by which it is rendered pathologically inadequate.

JOHNS HOPKINS HOSPITAL BULLETIN

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXXI is in progress. The subscription price is $3.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, $3.50 each.

A complete index to Vols. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

A STUDY OF THE CARDIOVASCULAR REACTION TO EPINEPHRIN

EPINEPHRIN SENSITIVENESS IN PATIENTS WITH HYPERTENSION

By Paul W. Clough

(From the Medical Clinic of The Johns Hopkins Hospital)

The possibility of utilizing as a diagnostic procedure the response of a patient to a subcutaneous injection of epinephrin was first brought to general notice by Eppinger and Hess.[1] They showed that in a number of cases, patients with Graves' disease responded to the injection of 0.001 g. of epinephrin with a marked rise in systolic pressure, tachycardia, mydriasis, glycosuria, and often with tremor, palpitation, and marked subjective nervous disturbances. Normal individuals, on the other hand, showed little or no response to this dose. Their claims that epinephrin sensitiveness is to be regarded as a fairly exact index of the tone of the sympathetic nervous system have not been entirely substantiated by subsequent observers, such as Barker and Sladen,[2] and Lehmann.[3] These later writers found, however, that in certain individuals, particularly in cases of thyroid intoxication, a state of marked epinephrin sensitiveness does exist.

More recently Goetsch[4] has advocated the use of the test as a diagnostic procedure in cases of thyroid intoxication, particularly in thyroid adenoma. He reported that after the subcutaneous injection of 0.5 c. c. of a 1-1000 dilution of epinephrin, a positive reaction was obtained with great uniformity in such patients, while in his experience it did not occur in individuals in whom thyroid intoxication could be excluded. He regarded a reaction as positive if a majority of the following symptoms developed: a rise of over 10 points in systolic blood pressure and in pulse rate, tremor, palpitation, throbbing of the peripheral vessels, flushing or pallor, asthenia, nervousness, anxiety, or an aggravation of previous subjective symptoms. His claims as to the frequency of positive reactions in thyroid intoxication seem on the whole to be receiving general confirmation, and the test is being used by some clinicians as a routine diagnostic procedure.

Peabody and his associates[5] employed the test in a study of soldiers with "irritable heart," and obtained positive reactions in 60 per cent of the cases. As these men did not show an increase in basal metabolism, as tested by Benedict's method, or definite clinical signs of thyroid disturbance, he did not regard the positive reactions as indicating increased thyroid activity.

Because of the increasing use of this test as a diagnostic procedure, it seemed desirable to put on record the observations included in this paper. The work was undertaken in order to study in detail the cardiovascular response to the drug, and to determine the frequency and degree of epinephrin sensitiveness in normal individuals and in a varied group of patients. Few cases of outspoken thyroid disturbance were included, but special attention was directed to patients with hypertension.

The patients were kept in bed for an hour or more before the test, and the blood pressure and pulse rate were recorded at frequent intervals until a constant level was established. A subcutaneous injection of 1 c. c. of a 1-1000 "adrenalin" solution * was then given, care being taken that the needle did not enter a vein. In some cases the dose was reduced to 0.5 c. c., 0.66 c. c., or 0.75 c. c. Observations of the systolic and diastolic blood pressure were taken at intervals of one minute during the first 5 minutes after the injection, and then at intervals of two or three minutes for 20 or 30 minutes, or until the reaction was definitely subsiding. Further readings were then taken at 5-minute intervals until the original level was reached. Care was taken to avoid unnecessary excitement or movement on the part of the patient.

The blood pressure was determined with a Tycos instrument by the auscultatory method. The diastolic pressure was read at the point at which there was an abrupt diminution in the intensity of the sound at the end of the third phase. The duration of the fourth phase was often prolonged after epinephrin injections, and the point of complete disappearance of the sound was usually 10 to 20 mm. lower. While attention was chiefly directed to the cardiovascular reaction, the occurrence of glycosuria, mydriasis, palpitation, tremor, and any form of subjective discomfort was also noted.

The slight pain and excitement associated with the injection often caused a rise of 10 mm. in the systolic blood pressure which usually subsided after 1 or 2 minutes. As a rule, the blood pressure showed little change during the first 5 minutes following the injection. There was then a fairly rapid rise in systolic pressure to a maximum, reached after from 10 to 20 minutes, and often associated with a simultaneous fall in diastolic pressure. There was then a more gradual fall in systolic pressure to the previous level or to a point somewhat below it, the latter being reached in from 45 to 90 minutes. The tachycardia and lowered diastolic pressure sometimes lasted considerably longer. In some cases in which absorption was presumably slower, the reaction consumed about double this time. In other cases the rise began after 2 minutes, and the maximum was reached after from 5 to 10 minutes. This must be explained by more rapid absorption.

After intravenous injection (Chart V) the maximum systolic pressure was reached within ½ to 1½ minutes, it fell rapidly after 2 or 3 minutes, and reached the previous level within 5 or 6 minutes.

For purposes of discussion the reactions observed have been divided arbitrarily into four groups, according to their

* Parke, Davis & Co.

intensity. In the first group were placed those cases giving a negative or insignificant reaction. The rise in systolic pressure was less than 15 mm. The rise in pulse pressure was less than 20 mm. and did not exceed 50 per cent of the initial pulse pressure. There were no subjective symptoms. This type of response was obtained in 40 per cent of all cases tested, and in 30 per cent of 32 normal individuals.

In the second group reactions classed as moderate were observed. In these cases (Chart I) there was a rise in systolic pressure of from 15 to 30 mm. and this was usually associated with a simultaneous fall in diastolic pressure of from 10 to 20 mm. There was therefore a marked rise in pulse pressure of from 25 to 40 mm. which amounted to from 50 per cent to 100 per cent of the initial pulse pressure. There was a striking change in the character of the sounds heard over the vessels; they became louder, very clear, and booming, so that it was easy to get sharp, accurate readings of both the systolic and diastolic pressures. The pulse rate usually rose 10 to 20 beats per minute. The tachycardia, as a rule, followed the rise in systolic pressure, often began only after the maximum pressure was reached, and reached its height after the pressure had fallen. As a rule, the subjective symptoms were slight. Glycosuria occasionally occurred. Moderate reactions occurred in 24 per cent of all cases tested, and in 50 per cent of 32 normal individuals.

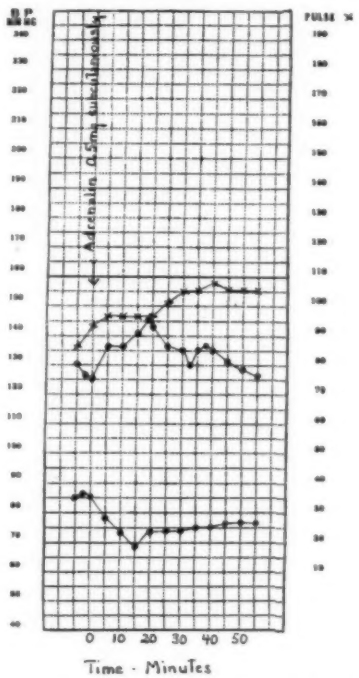

CHART I.—Moderate Reaction to Epinephrin.

Case No. 34723.—R. D., colored male, age 41.
Diagnosis: Myocardial insufficiency; chronic prostatitis.
There was a rise of 20 mm. in systolic pressure, associated with a fall of 18 mm. in diastolic pressure. The pulse pressure rose from 40 mm. to 75 mm., an increase of 87.5 per cent of the initial pulse pressure. The pulse rate increased 20 beats per minute, but the maximum rate was reached after the systolic pressure had fallen nearly to the initial level. There were no subjective symptoms.

In the third group of reactions, classed as marked (Chart II), there was a rise in systolic pressure of from 30 to 50 mm. In some of these cases there was also a fall in diastolic pressure, often very brief. In others the diastolic pressure rose with the systolic pressure, but this rise was much less than the rise in systolic pressure, and the increase in pulse pressure was always the striking feature. The increase in pulse pressure in this group was between 40 and 60 mm. or from 75 per cent to 200 per cent of its initial height. Pallor of the skin and mucous membranes was frequently observed. Such reactions were given by 23 per cent of all cases tested, and by 12.5 per cent of 32 normal individuals.

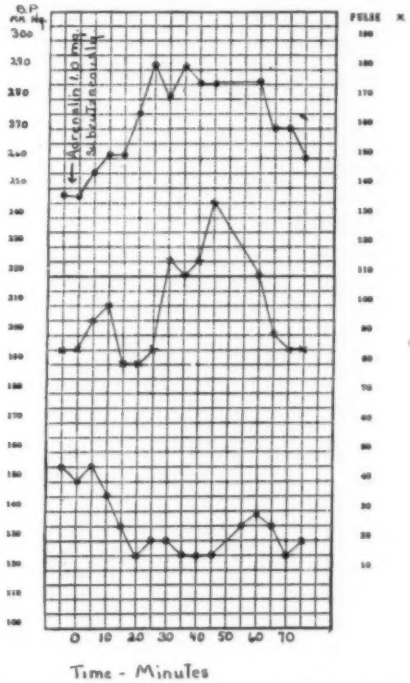

CHART II.—Marked Reaction to Epinephrin.

Case No. 33506.—E. N., colored male, age 58.
Diagnosis: Obesity, hypertension, myocardial insufficiency, chronic nephritis (?). No definite signs of hyperthyroidism.
On admission to the hospital the pulse was irregular in force and rhythm. Some beats were audible with a pressure of 310 mm. The patient was free from symptoms at the time the test was made.
The systolic pressure rose 45 mm., from 242 to 287 mm. The rise was more gradual than that shown in Chart III, the maximum being reached 30 minutes after the injection. The diastolic pressure fell 30 mm. The pulse pressure rose from 92 mm. to 167 mm., a rise of 75 mm., or 82 per cent of the initial pressure. The pulse rate rose from 80 to 130, but the maximum systolic pressure was reached before the rise began. The subjective discomfort was very marked. There was a rigor, sweating, polyuria, palpitation, extrasystoles, throbbing in the head, a "sick" feeling, mydriasis, and glycosuria of 5.5 g.

In the fourth group, giving very marked reactions (Chart III), the rise in systolic pressure was from 50 to 100 mm., while the pulse pressure increased about an equal amount, or between 75 per cent and 200 per cent of its initial height. Such reactions were obtained in 13 per cent of all cases tested, including 2 of 32 individuals regarded as physically normal.

In those cases showing a marked cardiovascular response, subjective symptoms were usually present. As a rule, these

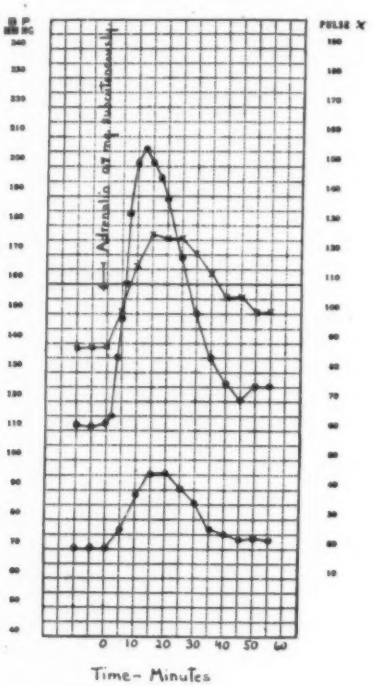

CHART III.—Very Marked Reaction to Epinephrin.

Case No. 34240.—H. C., colored male, age 68.

Diagnosis: Syphilis (Wassermann reaction), arteriosclerosis, hypertension, myocardial insufficiency. No signs of thyroid intoxication.

The blood pressure on admission was 150/100. At the time the test was carried out the symptoms of myocardial insufficiency were relieved, and the blood pressure was normal.

The systolic pressure rose 95 mm., reaching the maximum 12 minutes after the injection. The diastolic pressure rose 25 mm. The pulse pressure was nearly trebled, rising from 42 mm. to 112 mm. The pulse rate rose 40 beats per minute. Pulsus alternans developed during the reaction. There were nervousness and palpitation of moderate degree. No glycosuria.

patients complained of nervousness, palpitation, a sense of fluttering in the chest and throbbing in the head. Tremor was frequent, and in a few cases there was a violent chill. In the most severe reactions there was often precordial pain, anginoid in type, associated with great anxiety and marked subjective discomfort, difficult for the patient to describe. The palpitation, tremor, anxiety and discomfort sometimes occurred in patients giving only a moderate cardiovascular response, and the intensity of these symptoms was not in direct proportion to the circulatory changes. Glycosuria was often present, but it also did not parallel the blood pressure response. Hamman and Hirschman[1] have shown that the rise in blood sugar also does not parallel the rise in systolic pressure.

In one patient, who was suffering from thyroid intoxication with marked nervous manifestations,* a paradoxical reaction was observed. The blood pressure fell from 165/110 to 140/100 in the course of an hour. The pulse rate was unchanged, at 108 to 112. However, the sounds over the vessels became characteristically sharper and more thudding, and

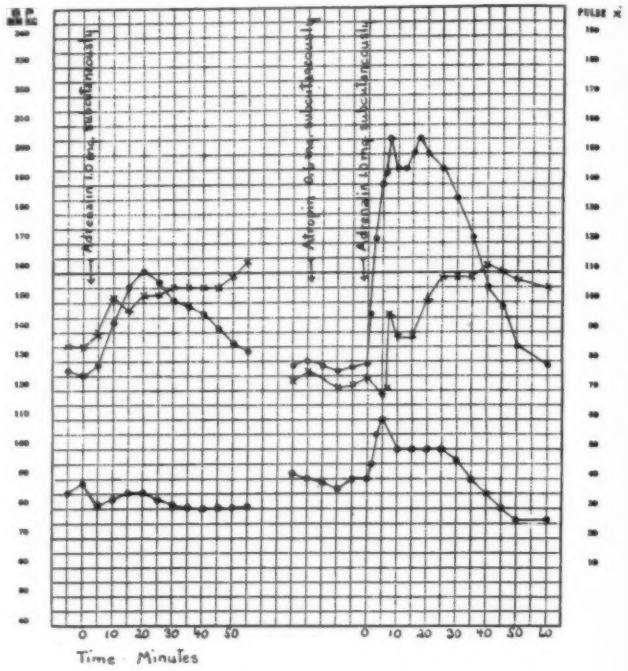
B.P. mm. Hg.
PULSE ×
← Adrenalin 1.0 cc. subcutaneously
← Atropin gr. ¹⁄₁₀₀ subcutaneously
← Adrenalin 1.0 mg. subcutaneously
0 10 20 30 40 50
0 10 20 30 40 50 60
Time - Minutes

CHART IV.—An Exaggerated Reaction to Epinephrin, Following the Administration of Atropin.

Case No. 34031.—J. M., colored male, age 34.

Diagnosis: Acute rheumatic fever; syphilis (Wassermann reaction). No signs of thyroid intoxication.

Following the injection of 1 mg. of epinephrin there was a fairly marked reaction, with a rise of 33 mm. in systolic pressure, and of 37 mm. in pulse pressure. Two days later, when the same dose was administered 15 minutes after a subcutaneous injection of 0.0006 gm. of atropin, a greatly exaggerated reaction was obtained. The systolic pressure rose 78 mm., from 122 mm. to 200 mm. The pulse pressure rose from 38 mm. to 105 mm., treble its initial height. The pulse rate rose from 70 to 110 per minute, but here also the maximum systolic pressure was nearly reached before the tachycardia began. The patient felt "nervous," and extra-systolic arrhythmia appeared. There were no other symptoms, no mydriasis, and no glycosuria.

there developed tremor and palpitation. The skin near the site of injection became very markedly blanched, and absorption was evidently very slow. It seems probable that this reaction is comparable to the results observed in animals, where a fall in blood pressure may follow the intravenous injection of a minute dose of epinephrin, which is not sufficient to cause a rise in pressure.

In several other cases a transient fall of 10 to 15 mm. in systolic pressure occurred 2 to 5 minutes after the injection,

* Seen through the courtesy of Dr. Emil Goetsch.

preceding a rise in pressure. This may be explained in a similar manner.

Atropin, administered hypodermically in doses of 0.6 to 0.8 mg. may cause a marked increase in the response to 1 mg. of epinephrin, given 10 to 15 minutes later, or it may cause a sharp epinephrin reaction in a patient who did not react to epinephrin alone. This is illustrated by the chart of J. M. (Chart IV.) Whereas 1 mg. of epinephrin caused a rise of 30 mm. in systolic pressure, a rise of 75 mm. occurred when the epinephrin injection was preceded by 0.6 mg. of atropin. Such an increased response is often associated with a rise in the pulse rate, but it cannot adequately be explained on that basis. As in this case the rise in blood pressure may precede the tachycardia, the maximum pressure may be reached or closely approximated before the rise in pulse rate begins, and the blood pressure is usually falling before the tachycardia reaches a maximum. Atropin seems to exaggerate the cardiovascular response to epinephrin without changing its character. Of 14 subjects tested, 8 showed an increased epinephrin response after atropin. It did not increase the tendency to glycosuria.

In bringing about this cardiovascular response, therefore, epinephrin must act in two ways; first, by causing a vaso-constriction of the small arteries, and secondly, by directly stimulating the heart, causing not only acceleration of the rate, but also augmentation of the force of the beat, and increase in the volume output. This direct stimulation of the heart seems to be the more important factor in the reaction. It seems impossible to find any other satisfactory explanation for the marked increase in pulse pressure, and particularly for the fall in diastolic pressure, so often associated with the increase in systolic pressure. Vasoconstriction alone could not do this. This view is supported by the visible precordial heaving, and by the sense of palpitation complained of during the reaction, which may be out of all proportion to the degree of rise in the systolic pressure.

In the more severe reactions vasoconstriction seems to play a more prominent rôle. Here the diastolic pressure also tends to rise, and there is often visible pallor of the skin and mucous membranes, while a sense of coldness of the skin is complained of by the patients. This is in accord with the well-known vasoconstricting action of the drug in animal experiments. The dose used in these clinical tests (0.015 to 0.02 mg. per kilo of body weight) is very small compared with the doses customarily employed in animal experiments, and exactly parallel results are not to be expected. Both the cardiac and the vascular responses are undoubtedly the result of stimulation of the sympathetic endings.

In all, tests were carried out on 95 subjects. Of these, 32 were either normal controls, or patients who were regarded as physically normal. Of these, 32 per cent gave negative reactions, 50 per cent moderate reactions, and 18 per cent marked reactions.

Individuals who were emaciated and cachectic, and who had a low blood pressure, especially if this was associated with diarrhœa or chronic organic disease, usually gave no response (80 per cent of 15 cases). Marked reactions were obtained in 4 patients, in whom the malnutrition and hypotension were associated with asthenia, nervousness, tremor, mental depression with irritability, and digestive disturbances. It is possible that thyroid intoxication may have played a rôle in these cases.

One of these patients gave a marked general reaction with rigor, palpitation, extrasystoles, precordial pain and oppression, and glycosuria. On attempting to repeat the test a few days later, the patient objected strongly to the test, and became greatly excited, so that the injection was not given. Nevertheless, there was a rise in blood pressure to about the same height as that reached in the reaction, and glycosuria again occurred. Apparently there had been an outpouring of endogenous epinephrin under emotional excitement.

In diabetes mellitus, slight or moderate reactions were obtained in 5 of 6 cases. In 8 cases showing marked evidences of endocrine disturbance other than hyperthyroidism, moderate or negative reactions were obtained.

One patient with amyloid disease, secondary to chronic pulmonary tuberculosis, gave no response to a subcutaneous injection of 1 mg. of epinephrin. However, a sharp rise of 50 mm. in systolic pressure followed the intravenous injection of 1 c. c. of a 1:10,000 dilution. Although this is a marked reduction below the average in sensitiveness, it nevertheless demonstrates that the vessels were capable of contracting.

The most striking finding was the frequency of marked reactions in patients with hypertension. A systolic pressure of 155 or over was adopted as a criterion of hypertension. However, a few patients have been included in whom a high blood-pressure reading was obtained on the first examination, although the pressure had fallen approximately to normal at the time the test was performed. Of 22 cases tested,* 15, or 68 per cent, gave marked reactions to 1 mg. of epinephrin, whereas such reactions were obtained in only 26 per cent of the 68 other cases tested, and in only 18 per cent of 32 normal individuals. This sensitiveness is shown more strikingly in the large percentage of very marked reactions observed, with a rise in systolic pressure of over 50 mm. Of the 22 cases of hypertension, 11, or 50 per cent, gave such reactions, while of 66 other cases (excluding exophthalmic goitre) only 2, or 3 per cent, so responded. Of the 15 cases of hypertension giving marked reactions, glycosuria was observed in 3 cases, mydriasis in 6, palpitation in 7, extrasystolic arrhythmia in 2, pulsus alternans in 1, and marked subjective discomfort or anxiety in 8. In several there was pallor of the skin and mucous membranes, and in 9 a rise in diastolic as well as in systolic pressure, indicating that vasoconstriction played a rôle in the reaction. Marked reactions were obtained, regardless of the degree, duration, or cause of the hypertension.

In none of these 15 cases were there any noteworthy "sympathicotonic" symptoms in the sense of Eppinger and Hess,

* Five subjects giving slighter reactions to smaller doses of epinephrin have been omitted because it was considered inadvisable to repeat the test in these individuals with a full dose.

nor were there signs of thyroid intoxication, unless it were slight protrusion of the eye-balls, widened lid-slits, and a positive lid-lag. Only 2 of the 15 cases showed definite evidence of any endocrine disturbance. One of these showed a slight degree of hypothyroidism, and the other the same condition in a very pronounced degree.

What is the significance of this epinephrin sensitiveness in patients with hypertension? Can it be used in support of the view that hypertension is the result of a suprarenal overactivity, of an hyperadrenalinæmia? To interpret correctly a pathological response to epinephrin we must have a thorough understanding of its pharmacological and physiological action. But, while the pharmacological action of epinephrin causing a stimulation of all the sympathetic nerve endings in the body is well established, the exact rôle which this substance plays in the normal physiological activities of the body is still unsettled. It is known that epinephrin is constantly being formed in the suprarenal medulla, and that it is secreted into the blood of the suprarenal vein. The general asthenia, low blood pressure, and enfeeblement of the circulation which occur in Addison's disease, and in experimental animals as a late result of removal of both suprarenal glands, in conjunction with other facts, have led many to the assumption that epinephrin serves to keep the sympathetic system, and in particular the cardiovascular structures which it innervates, in a state of constant activity or tone.[8]

This view is based on the assumptions: (1) That epinephrin is constantly present in effective quantities in the circulation, and (2) that the normal physiological action of epinephrin, in the concentration in which it is actually present in the blood, is qualitatively the same as that manifested by the relatively enormous doses used in animal experiments. For neither of these assumptions is there any conclusive evidence. The amount of epinephrin constantly present under "normal" conditions in the circulating blood has never been accurately determined. The most trustworthy estimates are based on a determination in animals of the concentration of epinephrin in the blood in the suprarenal vein, and a comparison of the rate of flow of blood in the suprarenal vein with that in the aorta. Such estimates made by Hoskins and McClure[9] indicate that the concentration of epinephrin in arterial blood cannot be much over 1 in 200,000,000, an amount not detectable by any known methods. Their estimates are substantially confirmed by the findings of Stewart and Rogoff.[10] Since epinephrin is rapidly removed from the blood and destroyed in its passage through the tissues, there is no opportunity for any appreciable accumulation in the blood. It is practically absent from venous blood.

Furthermore, it has been shown by Cannon and Lyman[7] that epinephrin in high dilution (though more concentrated than that probably present in normal blood) causes a vascular dilatation with a fall in blood pressure. Hence if epinephrin in the circulating blood normally exerts any effect on the vascular tone, it would presumably cause a depression rather than a stimulation.

The observations recorded in this paper, however, suggest that the minimal quantity of epinephrin required effectively to stimulate the human cardiovascular system is much smaller than might be expected from animal experiments. The writer found that 1 c. c. of a 1 to 50,000 dilution, injected intravenously, frequently sufficed to cause a distinct reaction with a rise in systolic pressure of 20 to 40 mm. (Chart V). In a man weighing 65 kilos, this quantity, if diluted with the estimated total blood volume, would give a concentration of approximately 1 in 200,000,000. The maximum possible "normal" secretion of epinephrin in animals, as estimated by Hoskins and McClure, would therefore be about equivalent

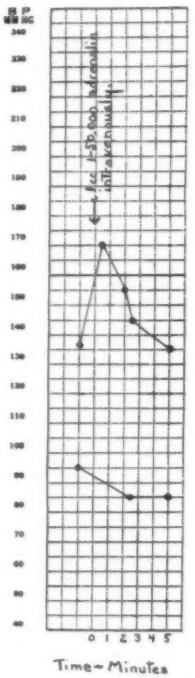

CHART V.—Moderate response to the intravenous injection of epinephrin.

Case No. 34901.—J. Q., white male, age 24.

Diagnosis: Acute nephritis; continued fever; tuberculosis of the spine. Slight renal insufficiency.

The dose was 1 c. c. of 1-50,000 dilution of epinephrin. There was a rise of 35 mm. in systolic pressure, reached about 30 seconds after the injection. The pressure fell practically to the initial level after 2½ minutes. The diastolic pressure was not accurately determined at the height of the reaction.

to this minimal stimulating dose in man. Several considerations, however, prevent one drawing any far-reaching conclusions from this parallelism. In the first place the epinephrin injected was not immediately diluted with the entire volume of blood, but reached the heart in a concentration considerably higher than 1 in 200,000,000. As pointed out above, the direct stimulation of the heart seems to be at least as important a factor as vasoconstriction in the milder reactions in man. Furthermore, if there be normally a continuous liberation of epinephrin into the blood, the effective stimulating dose is really the sum of that normally liberated into the

blood plus that injected. The additional quantity of epinephrin required to make effective a dose which is just subliminal may be a relatively small proportion of the total effective dose. Then again the normal rate of liberation in man may be different from that in animals.

More direct evidence that the maintenance of a normal blood pressure is independent of epinephrin liberation has been brought by Stewart and Rogoff.[11] These authors found that in cats, by removing one adrenal and cutting the nerves of the other, the normal liberation of epinephrin could be abolished or reduced to less than one per cent of the normal for many weeks, without impairing the health of the animals or affecting their blood pressure.

It seems well established, therefore, that epinephrin is not the direct means of maintaining blood pressure at the normal level.

It has been shown that the rate of liberation of epinephrin is under the control of the central nervous system, and evidence has been brought forward by Cannon and his associates [12] to show that in cats this secretion is subject to a marked temporary physiological increase under such emotion or exertion as is habitually encountered in the life of the animal. While the validity of Cannon's conclusions has been questioned, notably by Stewart and Rogoff [10, 11], there is strong evidence that under natural conditions a temporary outpouring of epinephrin may occur which is sufficient to produce symptoms and to cause a rise in blood pressure. As pointed out above, the quantity which suffices to do this is relatively small and well within the presumable capacity of the glands to secrete. It is quite conceivable, therefore, that under pathological conditions the secretion of epinephrin might be abnormally increased. If such an increase in epinephrin liberation occurred and persisted, the resulting overstimulation of the sympathetic endings might readily cause distinct symptoms of disease. Such a condition of increased secretion, it has been claimed, would give rise to a state of increased sympathetic tone (*sympathicotonie*), assuming that the effect of a pathological increase of epinephrin in the circulation would be a simple exaggeration of its supposed physiological action. Hypertension might be one manifestation of such a "sympathicotonic" state. This assumption received some apparent support from the demonstration by Kretschmer [13] that in animals blood pressure can be maintained at a high level by the slow continuous infusion of a dilute solution of epinephrin.

As a matter of fact nothing definite is known as to the occurrence or the effects of a persistent increase of epinephrin in the circulation. Experimentally it has not been possible to produce a condition of hyperactivity of the suprarenals. Repeated injections of epinephrin do not give rise to a comparable condition, because of the very transient action of the drug. Continuous infusions can only be maintained for a few hours at most.

There is no direct evidence of an increase of epinephrin in the blood in human disease. Such an increase was reported by Schur and Wiesel [14] in chronic nephritis with hypertension, but their results were not confirmed by subsequent observers. An increase was also reported in Graves' disease by Fraenkel,[15] by Kraus and Friedenthal,[16] by Bröking and Trendelenburg,[17] and by Adler.[18] All of these investigators used serum in their experiments and all except Adler applied it to test objects (frog's eye, rabbit's uterus, frog perfusion preparation) which respond to epinephrin by a contraction of smooth muscle. The validity of their results has been overthrown by O'Connor.[19] He showed that during the process of coagulation of the blood, substances entirely distinct from epinephrin appear, which cause a direct stimulation of smooth muscle, regardless of its innervation, and thus imitate the action of epinephrin. Citrated plasma did not manifest this activity. It is therefore necessary to use plasma and not serum in testing for epinephrin in the blood, or, if serum be used, to apply it also to test objects like strips of intestine [20] or coronary artery,[21] which respond to epinephrin by a relaxation and not by a contraction. Using the most sensitive method available, the frog perfusion test of Trendelenburg, O'Connor was able to detect epinephrin in plasma only from the blood of the suprarenal vein. He did not find any detectable epinephrin in the plasma from cases of Graves' disease.

These negative results are not absolutely conclusive, however, since these observers used venous blood in their investigations. A complete reinvestigation of this problem, using human plasma or serum obtained by arterial punctures would be very desirable, though it seems probable that the concentration of epinephrin even in arterial blood would be too small to be measurable by present methods.

The rate of liberation which would be required to maintain a hypertension is probably greater than the normal rate of secretion can be, and as pointed out by Hoskins and McClure,[22] would probably cause inhibition of intestinal peristalsis, glycosuria, and other disturbances of bodily function which are not present in hypertensives.

While Levy [23] found that in cats, with the thyroid intact, the administration of a single dose, or of several repeated doses of epinephrin, increased the response to a subsequent injection, Hoskins and Rowley [24] found that continuous infusions of epinephrin, regardless of whether or not they influenced the blood pressure, tended to diminish the response to an injection of an additional quantity of epinephrin, as well as to other forms of sympathetic stimulation.

The available evidence, therefore, does not support the conclusion that hypertension is due to, or associated with, a suprarenal hyperactivity, or a "hyperadrenalinæmia."

May this epinephrin sensitiveness in patients with hypertension be attributable to a state of hyperthyroidism, or thyroid intoxication? It was shown by Levy [25] that in cats any mode of stimulation of thyroid secretion increases the pressor effect of a subsequent injection of epinephrin. The association of epinephrin sensitiveness with unquestionable conditions of thyroid intoxication has been referred to. In some patients with hypertension there is a thyroid intoxication which is probably to be regarded as the cause of the hypertension. The latter symptom, however, occurs in a relatively small proportion of the cases of exophthalmic goitre or toxic adenoma,

and in the great majority of patients with hypertension there is no definite evidence of thyroid disturbance. It seems very doubtful if any such direct relationship between the two conditions exists.

It seems probable, therefore, that the increased sensitiveness to epinephrin injections in hypertension may be only one manifestation of a condition of increased reactivity on the part of the cardiovascular system to stimuli of all kinds. These patients often show an unusually marked change in blood pressure in response to exercise, emotion, or excitement. This sensitiveness might depend on an abnormal state of the sympathetic system, or the nerve endings, without assuming an overactivity of either the chromaffin system or of the thyroid.*

SUMMARY

There is a marked difference in the cardiovascular reaction of different individuals to a subcutaneous injection of 1 mg. of epinephrin.

The reactions observed has been classified arbitrarily, according to their intensity, as negative, moderate, marked and very marked. In a moderate reaction there was (1) a rise of from 15 to 30 mm. in systolic blood pressure, associated usually with (2) a fall of from 10 to 20 mm. in diastolic pressure. The striking feature of the reaction was (3) the increase in pulse pressure, which was often doubled. There was usually (4) a slight tachycardia. Other symptoms were usually slight.

In marked reactions the systolic pressure rose from 30 to 100 mm. There was usually a slight rise in diastolic pressure also, and a marked rise in pulse pressure. There was sometimes glycosuria, and very often tachycardia, palpitation, pallor, mydriasis, tremor, nervousness, and anxiety.

There must be two factors concerned in these reactions: (1) a direct stimulation of the heart, with increase in the force of the beat, and in the volume output, as well as in the rate; (2) constriction of the peripheral vessels. In the moderate reactions the first factor plays the chief rôle, whereas in the severe reactions vasoconstriction is also of importance.

Atropin frequently exaggerates the response to a subsequent injection of epinephrin.

Of 32 normal individuals 82 per cent gave a slight or moderate response.

Patients with hypertension often showed severe reactions to 1 mg. or less of epinephrin. Marked responses were obtained in 68 per cent of 22 cases, whereas they occurred in only 18 per cent of 32 normal individuals. This epinephrin sensitiveness occurred irrespective of the cause, the degree, or the duration of the hypertension. None of these patients showed evidences of significant endocrine disturbance.

It seems probable that this epinephrin sensitiveness in hypertension may be only one manifestation of a general abnormal reactivity of the cardiovascular system to stimuli of all kinds, and that it need not be attributed to a hyperactivity of either the chromaffin system or of the thyroid.

* As the dose of epinephrin used in these tests was larger than that recommended by Goetsch, these findings, of course, do not invalidate his claim that sensitiveness to a subcutaneous injection of 0.5 mg. indicates a state of active thyroid intoxication.

REFERENCES

1. Eppinger, H., and Hess, L.: Zur Pathologie des vegetativen Nervensystems. Ztschr. f. klin. Med., 1909, LXVII, 345-351; LXVIII, 205-230; 230-246.

2. Barker, L. F., and Sladen, F. J.: The clinical analysis of some disturbances of the autonomic nervous system, with comments upon the so-called vagotonic and sympatheticotonic states. Tr. Ass. Am. Physicians, Philadelphia, 1912, XXVII, 471-502.

3. Lehmann, G.: Was leistet die pharmakologische Prüfung in der Diagnostik der Störungen im vegetativen Nervensystem? Ztschr. f. klin. Med., 1914, LXXXI, 52-72.

4. Goetsch, E.: Newer methods in the diagnosis of thyroid disorders: pathological and clinical. N. York State J. M., 1918, XVIII, 259-267.

5. Peabody, F. W., *et al.*: Effects of the injection of epinephrin in soldiers with irritable heart. J. Am. M. Ass., 1918, LXXI, 1912-1913.

5. Peabody, F. W.: The basal metabolism in cases of the irritable heart of soldiers. Med. Clin. N. Am., 1918, II, 507.

6. Hamman, L., and Hirschman, I.: Studies on blood sugar. Arch. Int. Med., 1917, XX, 761-808.

7. Cannon, W. B., and Lyman, H.: The depressor effect of adrenalin on arterial pressure. Am. J. Physiol., 1912-13, XXXI, 376-398.

8. Biedl, A.: Die Nebennierensysteme. Die Innere Sekretion, Berlin and Wien, 1913, 2te Auf., I, 313-534; II, 1-76.

9. Hoskins, R. G., and McClure, C. W.: The adrenal glands and blood pressure. Arch. Int. Med., 1912, X, 343-356.

10. Stewart, G. N., and Rogoff, J. M.: The influence of certain conditions on the rate at which epinephrin is liberated from the adrenals into the blood. Proc. Soc. Exper. Biol. & Med., 1916-17, XIV, 77-79.

11. *Ibid.*: Quantitative experiments on the liberation of epinephrin from the adrenals after section of their nerves, with special reference to the question whether epinephrin is indispensable for the organism. Proc. Soc. Exper. Biol. & Med., 1916-17, XIV, 145.

12. Cannon, W. B.: The emergency function of the adrenal medulla in pain and the major emotions. Am. J. Physiol., 1914, XXXIII, 356-372.

13. Stewart, G. N., and Rogoff, J. M.: The influence of asphyxia upon the rate of liberation of epinephrin from the adrenals. J. Pharmacol. and Exper. Therap., 1917-18, X, 49-72.

14. Kretschmer, W.: Dauernde Blutdrucksteigerung durch Adrenalin und über den Wirkungsmechanismus der Adrenalin. Arch. f. exper. Path. u. Pharmakol., 1907, LVII, 423-440.

15. Schur, H., and Wiesel, J.: Ueber eine der Adrenalinwirkung analoge Wirkung des Blutserums von Nephritikern auf das Froschauge. Wien. klin. Wchnschr., 1907, XX, 699.

16. Fraenkel, A.: Ueber den Gehalt des Blutes an Adrenalin bei chronischer Nephritis and Morbus Basedowii. Arch. f. exper. Path. u. Pharmakol., 1909, LX, 395-407.

17. Kraus, F., and Friedenthal, H.: Ueber die Wirkung der Schilddrüsenstoffe. Berl. klin. Wchnschr., 1908, XLV, 1709-1714.

18. Bröking, E., and Trendelenburg, P.: Adrenalinnachweis und Adrenalingehalt des menschlichen Blutes. Deutsches Arch. f. klin. Med., 1911, CIII, 168-187.

19. Adler, L.: Untersuchungen über den Adrenalingehalt des Blutes. Deutsches Arch. f. klin. Med., 1914, CXIV, 283-291.

20. O'Connor, J. M.: Ueber den Adrenalingehalt des Blutes. Arch. f. exper. Path. u. Pharmakol., 1912, LXVII, 195.

21. Hoskins, R. G.: A consideration of some biological tests for epinephrin. J. Pharmacol. & Exper. Therap., 1911, III, 93-99.

22. Janeway, T. C., and Park, E. A.: The question of epinephrin in the circulation, and its relation to blood pressure. J. Exper. Med., 1912, XVI, 541-557.

23. Hoskins, R. G., and McClure, C. W.: The comparative sensitiveness of blood pressure and intestinal peristalsis to epinephrin. Am. J. Physiol., 1912-13, XXXI, 59-63.

24. Levy, R. L.: Studies on the conditions of activity in endocrine glands. IV. The effect of thyroid secretion on the pressor action of adrenin. Am. J. Physiol., 1916, XLI, 492-512.

25. Hoskins, R. G., and Rowley, W. N.: The effects of epinephrin infusion on vasomotor irritability. Am. J. Physiol., 1915, XXXVII, 471-480.

A CLINICAL STUDY OF THIRTY-NINE CASES OF COMBINED THORACIC AND ABDOMINAL WOUNDS

By GEORGE J. HEUER, Baltimore, Md.

In another paper we[1] have presented a study of 160 penetrating war wounds of the thorax and outlined, from a study of our series, the form of treatment which seemed to promise the best results. In that series were included fifteen cases in which we have either operative, X-ray, clinical, or autopsy proof that the diaphragm was perforated and some injury, although slight, to the abdominal viscera was sustained. The thoracic injury, however, far overshadowed the abdominal in severity, and because of this fact the cases were included in the penetrating thoracic wounds. In the present paper I shall study the combined thoracic and abdominal wounds, considering them, as I think they should be, as a special type of injury. For the sake of completeness in this study, I shall include the 15 cases above, and add to this number 24 cases not previously considered. Our series, then, consists of the following 39 cases:

(1) Twenty-one cases under my care at Evacuation Hospital No. 1. (2) Fifteen cases, operated upon by a group of surgeons at Evacuation Hospital No. 1 during September, 1918. The cases were seen and examined by me, then acting in the capacity of triage officer. After operation they were under my care. (3) Three cases treated at Base Hospital No. 18 at a time when it functioned as an evacuation hospital.

For convenience of study, these cases may be divided into three groups: a group of four patients moribund on admission, for whom no treatment excepting measures to combat shock was possible; a group of six patients not operated upon primarily but treated expectantly; and a group of twenty-nine patients subjected to immediate operation.

GROUP 1.—*Four Patients Admitted in a Moribund Condition.*—These were among the most seriously injured seen at an evacuation hospital. They were admitted in a condition of profound shock and with cough, hemoptysis, dyspnea, cyanosis, abdominal pain, and vomiting. On examination they presented open "sucking" chest wounds and signs of abdominal irritation. The chest wounds were immediately closed by strapping with adhesive, and the patients sent to the shock ward where the usual measures to combat shock were tried. In no case was there any response to shock treatment, and they died within a few hours after admission. Autopsy showed open chest wounds, lacerated wounds of the lower lobe of the lung, lacerated wounds of the diaphragm, and large lacerated wounds of the liver, stomach, or colon. In no case did autopsy indicate that there was hemorrhage sufficient in itself to account for death; indeed, hemorrhage was rather insignificant. Death was due presumably to shock, the result of open pneumothorax and extensive wounds of important organs.

GROUP 2.—*Six Patients Not Primarily Operated Upon.*—In this group there were two bullet wounds and four shell wounds; five were penetrating wounds with retained missiles (of which four were shell fragments, one a bullet) and one a perforating wound with wound of entrance and exit; all were closed wounds. In character the wounds were all punctured wounds without extensive laceration of the soft parts and in only one instance with a moderately extensive rib fracture. In position the wounds were all upon the right side of the body. Five were pure thoracic wounds, the wounds of entrance located upon the lateral thoracic wall between the fifth and eighth ribs in four cases; upon the posterior thoracic wall at the level of the tenth rib in one case. One was a perforating wound, the wound of entrance upon the right back below the costal margin, the wound of exit at the level of the seventh rib just lateral to the right nipple line. The most common wound, therefore, was the shell wound which penetrated the lateral thoracic wall between the fifth and eighth ribs and coursed obliquely downward and inward. The foreign body in the five cases with retained missiles was lodged in the liver in four cases, in the thorax and against the spine in one case. In size, two shell fragments were over 1 cm. but less than 2 cm. in diameter; two were less than 1 cm. in diameter. In one case a machine-gun bullet had been retained.

Shock was profound in two cases, moderately severe in two cases, and practically absent in two cases. Under appropriate measures shock was recovered from in all the cases.

Hemothorax was massive and associated with marked cardiac displacement in two cases; of moderate grade (reaching the angle of the scapula) in four cases. Aspiration of 1000 c. c. of blood on three successive days for mediastinal compression symptoms was necessary in one case.

Symptoms and signs of abdominal irritation were present in three cases, absent in three cases. In two cases the symptoms and signs were upper abdominal pain and tenderness and rigidity chiefly of the right upper quadrant; in one case the abdomen was retracted and rigid, resembling the abdominal picture of an acute perforation of a hollow abdominal viscus. In none of the cases was there hiccup or vomiting.

Clinical Course.—Only one patient in the series pursued an uncomplicated course to recovery. The remaining five patients developed infectious complications. Three patients developed infected hemothorax, two of whom were treated by rib resection and drainage with subsequent sterilization of the cavities; one by repeated aspirations. All of the three recovered. One man with multiple serious wounds in addition to his thoracic injury, developed gas gangrene of the left leg for which a thigh amputation was done. He died with all the symptoms of gas intoxication. At autopsy, a clinically unsuspected abscess of the middle lobe of the lung was found about a bone fragment. The foreign

[1] Heuer, Pratt and Mason: A clinical study of 160 penetrating war wounds of the thorax. To be published in the Annals of Surgery, November, 1920.

body was embedded in the liver and perfect healing had taken place. One patient developed a lobar pneumonia involving the upper and lower lobe of the lung contralateral to the injury, from which he died. At autopsy perforating wounds of the right lower lobe of the lung, of the right lobe of the liver, and the upper pole of the right kidney were found. There was no reaction about these wounds. The infectious complications in all these cases, therefore, were entirely referable to the thoracic wounds, in no instance to the abdominal injuries.

Treatment.—The treatment in this group was the same as that for simple thoracic injuries. Rest in bed, morphin when necessary and aspiration for the treatment of hemothorax, were the measures employed until infectious complications appeared. Aspiration for the hemothorax was performed in four cases, not performed in two cases. Infected hemothorax was treated by rib resection and drainage in two cases, one of which was a gas bacillus infection. A third patient, in whom the streptococcus viridans was the infecting organism, was treated by repeated aspiration and recovered without the development of a frank empyema.

Results.—One patient recovered without complications; five patients developed infectious complications, of which three recovered and two died. Mortality, 33⅓ per cent.

Group 3.—*Twenty-Nine Patients Subjected to Immediate Operation.*—In this group there were 28 shell wounds, one bullet wound; 27 were penetrating wounds with retained missiles, two were perforating wounds. Twenty-seven were thoracic wounds—of the right thorax in 17 instances, of the left in 10 instances; two were abdominal wounds which had penetrated the thorax. Of the thoracic wounds, 10 were open and sucking, 17 were closed.

The position of these wounds will be indicated in the following paragraphs. In character, the wounds varied from large lacerated open wounds with extensive rib fractures, to small closed wounds without much tissue destruction. Ten of the thoracic wounds, as above noted, were large open sucking wounds, 17 were small punctured closed wounds. Extensive rib fractures (from one to five ribs) occurred in thirteen cases, ten of which had open sucking thoracic wounds. The missiles producing these wounds were single in 24, multiple in five cases. In three of the five cases two foreign bodies were present, in one case three foreign bodies, and in one case four foreign bodies. They were lodged in the abdomen alone or in the chest and abdomen. It is rather interesting to note that two, three, and four missiles may produce and penetrate through a single wound, and the failure to recognize this fact may result, as in one of our cases, in overlooking an important lesion. In size the missiles varied from small shell fragments to fragments 2.5 cm. in diameter. In one instance a machine-gun bullet was retained.

Shock was a striking feature in the majority of these patients on admission. Profound shock necessitating preliminary shock treatment before operation was undertaken, was present in sixteen cases, a moderate grade of shock in nine cases, little if any shock in four cases. From our operative findings it would appear that hemorrhage—never excessive—was but a slight contributing factor in the production of shock, but that the degree of shock bore a definite relation to the presence of open pneumothorax and to the extent of the lesions of important organs.

Physical Examination.—The physical examination in these cases showed the symptoms and physical signs common to penetrating thoracic wounds and to abdominal wounds. In the right-sided injuries, hemothorax if the external wound was closed, or hemopneumothorax if it was open, was invariable in this series. The hemorrhage occurred from the lung alone, from the lacerated liver alone, or from both lung and liver wounds. The usual symptoms of cough, hemoptysis, and dyspnea were present in varying degree. The abdominal signs were those of upper abdominal pain, tenderness and rigidity. But in cases in which a bleeding liver wound gave rise to an excessive hemoperitoneum, general abdominal rigidity, even a boardlike abdomen, was present. Hiccup and vomiting were infrequent in the right-sided injuries; but occurred when the liver was perforated and additional lesions within the abdomen were produced. Bloody urine was present when the right kidney was injured. In these as well as in the left-sided injuries, the laceration of the diaphragm may actually be seen when the external thoracic wound is large. In the left-sided injuries the same signs and symptoms common to thoracic wounds were present; but the abdominal signs due to more frequent injury to hollow abdominal viscera were more marked. Vomiting, in addition to abdominal pain, tenderness and rigidity, was present in all cases in which hollow viscera were perforated; in part due perhaps to the perforation *per se*, in part no doubt to an early peritonitis from leakage of stomach and intestinal contents. It is remarkable, however, to observe, as in three of our cases of left-sided injury, that the abdominal viscera may entirely escape injury, even when the course of the missile, as determined by the external wound and the location of the foreign body, is such that escape from injury seems impossible.

Herniation of the abdominal viscera through the wound in the diaphragm occurred quite commonly in these injuries. In the right-sided injuries it was uncommon, was always of the liver, and only when the wound in the diaphragm was extensive. In the left-sided injuries, herniation of a bit of omentum was always found in the punctured wounds of the diaphragm. In the large wounds of the diaphragm, herniation of a part of the stomach, the colon, the spleen, or the small intestine occurred. In one case the omentum was prolapsed through the external thoracic wound at the level of the seventh rib. Gastric and intestinal contents were commonly found mixed with the hemothorax when the stomach or intestines were perforated. In one case gastric contents were expelled from a high thoracic wound with each act of vomiting.

The diagnosis of diaphragmatic hernia before operation was possible only in the case of external hernia and in those cases in which the diaphragm could actually be seen through the external wound. In the presence of hemothorax, the diagnosis of diaphragmatic hernia is obviously difficult both by physical and X-ray examination.

Treatment.—The treatment of these cases was by operation as soon after admission as their condition warranted it. For the sake of avoiding confusion it may be well to describe the operative procedures separately in the right-sided thoracic wounds, the left-sided thoracic wounds, and the abdominal wounds.

(1) *Right-Sided Thoracic Wounds (17 Cases).*—The wounds of entrance were upon the lateral thoracic wall in eleven cases, upon the anterior wall in three cases, and upon the posterior wall in three cases. The general course of the missiles, therefore, was downward and mesialward in the majority of cases, or backward and downward, or forward and downward. Six were open sucking wounds, eleven were closed wounds. Foreign bodies were localized in the liver alone in six cases, in the lung or pleural cavity alone in two cases, in the abdominal cavity alone in three cases. Multiple foreign bodies were localized in the pleura and liver in two cases, in the pleura and abdominal cavity in one case. In three cases the location of the foreign bodies is not accurately stated. In two cases the wounds were perforating and without retained foreign bodies.

In general the operative procedures in this group of cases consisted of a transpleural exploration, a transperitoneal exploration, or a combined transpleural and transperitoneal exploration. The choice of procedure depended upon the character and position of the external wound and our ability to diagnosticate abdominal lesions. In the presence of open sucking thoracic wounds, these always took precedence and the primary operation was carried out through the thorax, to be followed by an abdominal laparotomy

if conditions warranted. In the low wounds of the back or loin, abdominal exploration was carried out first and followed or not by thoracotomy as seemed indicated. Thoracotomy or transpleural laparotomy was done alone in eleven cases, abdominal laparotomy alone in one case, a combined transpleural and transperitoneal exploration in five cases (primary thoracotomy followed by laparotomy, three cases; primary laparotomy followed by thoracotomy, two cases). Transpleural laparotomy consisted in débridement of the wound of entrance, resection of 10 to 12 cm. of a single rib, exploration of the pleural cavity, evacuation of the hemothorax, removal of missiles and bone fragments from the pleura and lung, débridement and suture of wounds of the lung, incision of the diaphragm in the direction of its fibres, exploration of the liver, removal of the foreign bodies from the liver, and suture of liver wounds. When control of bleeding from the liver was unsatisfactory by suture, tamponade of the liver wound was done, the tampon being brought out through the thoracic wound after suture of the diaphragm to the parietal pleura. The technic of abdominal laparotomy requires no comment. In this series of cases the lesions found were as follows: *Hemothorax* was present in every case, in the majority of slight or moderate grade. The *lung*, aside from small lacerations due to rib fragments or small missiles requiring no special treatment, escaped serious injury in fifteen cases; the lower lobe was perforated in one case; the middle and lower lobes extensively lacerated in one case. Injuries to the *diaphragm* were invariable. The wounds varied from small punctured wounds to lacerated rents 10 cm. in length through which the convex surface of the right lobe of the liver herniated into the pleural cavity. The liver was injured in every case, the wounds being either perforating wounds (2 cases); penetrating wounds with retained missiles (8 cases); or lacerated wounds of the convex surface of the right lobe varying in size up to 10 cm. in length (7 cases). A considerable hemoperitoneum was demonstrated in five cases, but no doubt this condition was present in a larger number of cases. The small intestine was perforated in one case. Closure of the wounds was done without drainage or tamponade in seven cases; tamponade of liver wounds was deemed necessary in eight cases, the tampon being brought out through the thoracic wound; the parietal wounds were drained in two cases. The abdominal cavity was not drained.

Results.—Of the 17 patients in this group, nine recovered and eight died, a mortality of 47 per cent. One died upon the operating table, seven died from shock within twenty-four hours of the operation. Of the nine patients who recovered, eight escaped complications and were discharged apparently well. One man developed an infected hemothorax, but recovered after drainage of the pleural cavity.

(2) *Left-Sided Thoracic Wounds (10 Cases).*—The wounds of entrance were upon the left lateral thoracic wall in eight cases, the anterior thoracic wall in one case, and the posterior thoracic wall in one case. The course of the missiles was, therefore, downward and mesialward in the vast majority of cases. Four were large open sucking wounds and one a small sucking wound; five were closed wounds. Foreign bodies were localized in the abdominal cavity alone in eight cases, in the parietal thoracic wall in one case, in the abdominal and thoracic walls in one case. There were no perforating wounds in this group.

The operative procedures were in general similar to those in the preceding group. In open sucking chest wounds, thoracic exploration always took precedence and was followed by laparotomy if indicated. Thoracotomy with abdominal exploration through the diaphragm was done alone in seven cases, thoracotomy followed by laparotomy in three cases. The technic of the procedures was the same as in the preceding group. In two cases incomplete operations were done. In one, owing to the profound shock, nothing more than the operative closure of an open thoracic wound was done, although the likelihood of an abdominal lesion was recognized. The patient died the day following operation and at autopsy a perforation of the transverse colon with peritonitis was found. In the other a frank operative blunder was made. Two missiles entered the lateral thoracic wall through a single wound of entrance; one apparently was deflected by a rib and was embedded in the muscles of the lateral abdominal wall; one penetrated the thorax. There were signs of abdominal irritation. A thoracotomy was done and the dome of the diaphragm examined. We quite failed to find a wound of the diaphragm and assumed, although we did not find it, that the foreign body was in the pleural cavity. The abdomen was not explored. The patient died of peritonitis, and even at autopsy the wound of the diaphragm was found with difficulty.

The lesions found at operation in this group of cases were as follows: *Hemothorax* was invariably present. In the majority of cases the amount of blood was small. It was macroscopically mixed with stomach or intestinal contents in three cases. The *lung* was extensively injured in two cases; escaped injury in eight cases. The *diaphragm* was invariably injured, the wounds varying from small punctured wounds to large lacerated wounds. In the small punctured wounds a bit of omentum with one exception was found herniated through the diaphragmatic opening. In the larger wounds, a part of the spleen, stomach, or transverse or splenic flexures of the colon in addition to the omentum was found herniated into the pleural cavity. Perforating wounds of the stomach alone were found in two cases, of the colon alone in three cases, of the spleen alone in one case. Two perforating wounds of the lesser curvature of the stomach, together with a grooving lacerated wound of the liver, was found in one case. Operation for abdominal lesions consisted in suture of the perforating wounds of the hollow viscera and splenectomy—in the majority of cases done through the thoracic incision. In only one case was a fibrinopurulent peritonitis present at the time of the operation. In three cases, although the foreign bodies were found lying free in the abdominal cavity, no intra-abdominal injury aside from slight traumatism to the omentum was found. Closure of the wounds was without drainage in six cases, with drainage in four cases.

Results.—In this group four patients recovered without complications and were discharged well. Six patients died, a mortality of 60 per cent. Three patients died within twelve hours after operation from shock, two died within thirty-six hours after operation from shock and peritonitis, one died two days after operation from peritonitis. Every patient in this group with the perforation of a hollow viscus died; every patient without the perforation of a hollow viscus recovered.

(3) *Abdominal Wounds (2 Cases).*—The wounds of entrance were upon the anterior abdominal wall just to the right of the epigastric angle in one case, upon the lateral abdominal wall in the other. In the first case the missile coursed upward and to the left, lacerating the concave surface of the right lobe of the liver, perforating the lesser curvature of the stomach, lacerating the spleen, perforating the diaphragm and lower lobe of the left lung, fracturing the ninth rib, and lodging under the skin of the lateral thoracic wall. In the second case, four missiles entered through a single large wound and extensively lacerated the right kidney. One foreign body penetrated the abdominal cavity, three perforated the diaphragm and remained in the right pleural cavity. Operation in the first case, owing to the profound shock, was an incomplete one and consisted of abdominal laparotomy, suture of the liver, suture of the perforation in the stomach, and tamponade of the spleen. The wound in the diaphragm was not treated, nor was the thorax opened. The foreign body was not removed. In the second case operation consisted in a right nephrectomy and an exploratory laparotomy with removal of the foreign body. The thorax was not opened.

Results.—Both patients died, a mortality of 100 per cent. In both cases death occurred within twelve hours after operation from shock.

SUMMARY

Of the entire series of thirty-nine patients seventeen recovered and twenty-two died, a total mortality of 56 per cent. Excluding the four patients moribund on admission, the mortality is 46 per cent. Analyzing the results from the standpoint of known injuries to solid and hollow abdominal viscera, we find that the mortality, when solid abdominal viscera alone are injured, is 40 per cent; when hollow abdominal viscera are injured, it is 86 per cent.

THE NATURAL HISTORY OF TYPHOID FEVER IN BALTIMORE, 1851-1919*

By William Travis Howard, Jr.

INTRODUCTION

In discussions on the course of typhoid fever in any community over a considerable number of years, it has been the custom to assume that there have been, during the periods under study, at least four constants: First, that, on the whole, the population has remained constant in regard to susceptibility to the disease when exposed; second, that both the invasive and the killing capacities of the causal agent have been, on the average, the same; third, that the honesty and the diagnostic acumen of physicians, as well as the available methods of diagnosis and the clinical course of the disease have all remained relatively unchanged; and fourth, that the results of the medicinal treatment and management of cases of the disease have undergone no important variations. As a matter of fact, in most communities at least, such an assumption is unwarranted, and Baltimore is no exception to the general rule that variations in all these factors have taken place between 1851 and 1919, the period covered in the present study.

The population has been under a continual change; one not attributable to loss by death and replacement by birth. New racial elements have entered, and a larger proportion of those born now reach the typhoid age than in former years. Just before our period opens, and running well into its first twenty-five years, there was a large immigration of Irish and of Germans which raised these stocks to a much greater proportion of the population than had obtained previously. Such interesting race stocks as the Russian and Polish Jew, the Czech, the Lithuanian, the Polish, and the South Italian have all joined us since the date when the typhoid rate began to decline. Representatives of other races in smaller numbers have come in more recent times. The numerical proportion of negroes to whites in the population has remained relatively unchanged at one-sixth. Have the immigrants added to or subtracted from the proportion of our typhoid susceptibles? The important questions of the transmission of either typhoid susceptibility or non-susceptibility to the progeny of those who survive attacks of the disease and of the value to be set upon the elimination of typhoid susceptibles through death from this or from other diseases are wholly ignored.

It has been the habit to assume, at least tacitly, that each city has its own typhoid bacillus strain of unvarying infective and lethal capacities. This is far from true, for additions of new races, or strains, of typhoid bacilli are being brought in continually, often from distant parts of the world, and are being diffused; again, old ones are perhaps changing their characteristics or even dying out. It is by no means certain that case fatality rate among typhoid fever cases is in any place, whether it is an open or a closed community, constant over any considerable period of time. In fact, there is much evidence that the contrary is true.

Nor is it possible to estimate accurately the influence of diagnosis, or of fashion in diagnosis, upon typhoid death rates. Bilious fever and malarial fever as causes of death died hard. Pathological anatomists are familiar with the wide margin of error in the diagnosis of typhoid fever. They have found only too often the lesions of this disease and the typhoid bacillus in bodies coming to the autopsy table with diagnoses of pneumonia, empyema, meningitis, tuberculosis (especially general miliary), appendicitis, acute endocarditis, influenza, uræmia, etc., and perhaps the reverse has been experienced as often. Intelligent health officials are well acquainted with these sources of error. In 1919, physicians in Baltimore withdrew the diagnosis of typhoid fever, reported by them to the Health Department, in 42 cases, the most common diagnosis substituted being pneumonia, empyema, influenza, intestinal intoxication, and tuberculosis. Some of these patients had been sent to hospitals by practitioners as cases of typhoid fever. On the other hand, in a considerable number of instances, cases of typhoid fever were first reported as pneumonia or as influenza. Again, it is only comparatively recently that paratyphoid fever has been elevated to the position of a separate disease, and even now while para-typhoid and typhoid fevers, as reported cases, are classified separately in the Health Department records, deaths from the former are still charged to the latter in the international classification.

The question whether the larger experience given physicians during the former period of greater prevalence of typhoid fever did not counterbalance the influence of the more refined methods now available is at best an open one. Outside of exceptionally well organized hospitals, the blood culture method of the diagnosis of typhoid fever is relatively seldom used. Every public health administrator who has carefully

* Papers from the Department of Biometry and Vital Statistics, School of Hygiene and Public Health, Johns Hopkins University, No. 15.

studied the subject must be aware that, under the conditions which must of necessity obtain in its application and interpretation, the Widal reaction is often a source of error. When a single test is relied upon, many cases of typhoid are excluded, and, in numerous instances, cases of other diseases are classed as typhoid. This is due in the main to three sources of error: the use in the diagnostic laboratories, year in and year out, of a single strain of *B. typhosus*, usually one that is highly sensitive to human serum; the fact that the degree of dilution of the serum is mere guess-work, depending not only upon the bacteriologist's judgment in color, but upon the relative amount of coloring matter in a given amount of the blood of the subject of the test, *i. e.*, his degree of anæmia or plethora; and the fact that in several acute affections, notably influenza, endocarditis, and miliary tuberculosis, which are most apt clinically to be confused with typhoid fever and to suggest to the physician the advisability of appealing to the Widal reaction, the blood serum often acquires the property, even in considerable dilution, of agglutinating *B. typhosus*. These considerable sources of error, while known to many public health bacteriologists, are not so well appreciated by many practising physicians and public health administrators. In a large proportion of the 42 cases of withdrawn diagnosis of typhoid fever above alluded to, the attending physicians were misled by positive Widal reactions. Notwithstanding these drawbacks, the Widal reaction, as applied under the relatively unfavorable conditions inherent to public health laboratory service, is of great service to both practising physician and public health administrator and has undoubtedly promoted accuracy of diagnosis. The laboratory of the Health Department has perhaps been the most effective agent in rectifying the old confusion of malaria with typhoid fever in Baltimore. That some physicians have a habit of burying their fatal cases of continued fever under the diagnosis of typhoid fever is well known in the Health Department. The affections sought to be covered under typhoid fever as a cloak are especially puerpural fever, surgical infections, and tuberculosis.

My impression, after four years experience and a study of the records of the Health Department, is that, on account of errors in diagnosis and deliberate misstatements on death certificates, the number of registered deaths from typhoid in Baltimore are certainly below the actual number in the earlier period and probably above it in the later period covered by this study. This is, however, to some degree, balanced by my inclusion of deaths registered as due to typho-malaria with deaths from typhoid fever.

Many facts lead to the conclusion that under the influence of the great improvement in living conditions, using the term in the broad sense to cover improvements in hospitals and in nursing, the substitution of bathing and sponging and of the expectant for the drastic treatment of typhoid fever that has marked the last thirty years, the physician has been able, on the whole, greatly to improve the typhoid patient's chances of recovery.

Though the knowledge necessary for the proper evaluation of these and perhaps other important factors of error is lacking, attention is directed to them, for, so far as I am aware, in discussions such as the present one, they have been left out of consideration, and it has been very generally assumed as true that the forces of morbidity and mortality of *B. typhosus*, on the one hand, and the material upon which they act, on the other, have remained constant. With the exception of some figures on the white and colored and on the two sexes, there are now available no satisfactory data for a study of the genetic relationships of typhoid fever in Baltimore. This study covers, then, for the most part, a consideration of some of the environmental relationships of typhoid fever in the population of Baltimore from 1851 to 1919, inclusive.

The morbidity and mortality figures, the case histories, and much of the general data were obtained from records of the Health Department, and for these I am under deep obligation to Dr. C. Hampson Jones, Commissioner of Health, Dr. John F. Hogan, Assistant Commissioner of Health, Dr. William Royal Stokes, Bacteriologist, Dr. Marion B. Hopkins, Chemist, Mr. Moore and Miss Betz of the Division of Statistics, and Mrs. Bertha M. Muller. To the Health Wardens and to the Nursing Staff I am indebted for histories of reported cases.

The population figures used in obtaining morbidity and mortality rates are not those of the Bureau of the Census. They were calculated by Mr. John Rice Minor, at the suggestion of Dr. Raymond Pearl, by fitting a logarithmic curve to the population figures of Baltimore, as given by the Bureau of the Census for the censual years. These population figures, representing more accurately, it is believed, than those given by the Bureau of the Census, the populations of both censual and intercensual years, are used constantly in this laboratory in work on the morbidity and mortality data of Baltimore. As the population figures are somewhat higher than those of the Bureau of the Census, the rates are somewhat lower, particularly in the latter years, than those of the Health Department and of the Bureau of the Census.

THE EARLY HISTORY OF THE COURSE OF TYPHOID FEVER IN BALTIMORE

Typhoid fever was not recognized officially by the Health Department as a cause of death until 1851. It was probably hidden under the terms bilious, malarial, typhus, nervous, and gastric fevers, and diarrhœa and dysentery in the early years of the Town and City, and during this period bilious, typhus, and malarial fevers were all accredited with a considerable number of deaths. Nervous fever appears as a cause of death in from 1 to 9 cases in each year from 1812 to 1824. Gastric fever was first given as a cause of death in 1837, and the number of deaths from this affection gradually increased from 3 in 1837 to 30 in 1850, after which this cause declined. Bilious fever was given as a prominent cause of death from 1812, the earliest date to which I can refer, with 99 deaths. It declined to 53 deaths in 1852. It is credited, however, with 72 deaths in 1853. By 1875 it had declined to 1 death and entirely disappeared after 1885.

It is interesting that Thomas H. Buckler, William Power, William T. Howard, Frank Donaldson, Christopher Johnson,

J. W. Houck, Charles Frick, and others, including medical students at the Almshouse, were familiar with the clinical course and anatomical lesions of typhoid fever in the early 40's. Buckler and Power were visiting physicians, and the others mentioned were resident physicians, to the Almshouse and its Infirmary as early as 1843. J. K. Mitchell and other professors of medicine clearly recognized the disease in their lectures and writings in the 40's. It was, however, not until after William Jenner's paper, read on December 11, 1849, before the Royal Medical and Chirurgical Society of London, that the Health Department included typhoid fever as a cause of death. This is the more curious because William Power, generally recognized as the leading clinician of his time in Baltimore, was a pupil of Louis from 1835 to 1838, and was Professor of the Practice of Medicine at the University of Maryland in 1846. Bartlett, who preceded him in the Chair of Practice, was thoroughly familiar with not only the work of Louis, but that of Shattuck in London, Stewart in Glasgow, in 1839 and 1840, and Gerhart in Philadelphia, in 1837, and published his epochal book on continued fevers in 1842. In 1851, Thomas H. Buckler recorded that a very grave form of typhoid fever prevailed among the inmates of the City Almshouse in 1846, 1847, 1848, 1849; that in the latter three years the wards were never free from the fever; and that the resident physicians and students in the Infirmary rarely escaped the disease. Buckler did not mention the degree of prevalence of typhoid fever in the City proper, but he stated that Dr. Frank Donaldson had demonstrated the intestinal lesions of typhoid fever in an immigrant at the Quarantine Hospital in 1847. In the same year, two immigrants with typhoid fever were sent from an immigrant ship to the Almshouse Infirmary. The reports of the Quarantine Officer about this date not infrequently mention cases of typhoid fever.

In the tabulation of the medical and surgical cases treated in the infirmary of the Almshouse in 1828-1829, there were recorded 58 cases, with 13 deaths, of *febris typhoides*. The term *typhoid fever* was first used in the annual report of the Almshouse in 1833, when there were 13 cases and 3 deaths. The annual reports of the attending physicians recorded cases of typhoid fever every year from 1833 to 1849, inclusive, with the exception of 1837. In these seventeen years, there were 359 cases and 106 deaths, with a case fatality rate of 29.53 per cent.

The earliest date of the appearance of the disease in Baltimore is unknown. It was perhaps introduced early and became increasingly prevalent during the enormous growth of the City between 1790 and 1830. It is practically certain that a great many cases of this fever reached Baltimore in the early 40's and early 50's among the great crowds of Irish immigrants who brought typhus and smallpox as well. It is likely that typhoid fever gained a hold in the City at an early date and spread in the usual ways, but especially by pollution of springs and wells and milk and by the mediation of flies, favored by the constant overflowing of the crude privies and privy wells. It is probable that in its earlier days the Lake Roland water supply was not seriously contaminated. With the increase of the suburban population on this water shed, and later on the Gunpowder water shed, these water supplies became very seriously contaminated. In the meantime, the city springs and wells became more and more polluted, the privies became more dangerous, and milk became a very grave menace.

GENERAL SANITARY CONDITIONS IN 1850

In regard to sewers and the disposal of night-soil from privies and privy wells, the foul pictures given in the report of Wynne in 1849 and the reports of the Health Department from this date until a relatively recent period could only be duplicated in the London of the beginning of the 19th century. Harford Run and Jones' Falls to the east and Chatsworth Run and Schroeder's Run to the west duplicated in their foulness the old Fleet and Holborn sewers of London. The Basin into which these filth-streams emptied was perhaps worse than the Thames. It was so foul, that, according to Thomas H. Buckler, as late as 1875 its rotten egg odor commonly reached "Evergreen," his place just north of the present North Avenue, and with a favorable south wind it was clearly detected at Towson. The privies and privy wells in yards and even in the cellars of some of the best houses were constantly overflowing into cellars, courts, lanes, alleys, and streets. The low-lying parts of the City, at Fells Point, along the outlet of Jones' Falls, in the section bordering on the Basin, and the southwest section near Spring Gardens, were in a constant state of nuisance, and large portions of these districts were subject to flooding after very heavy rains. The higher section, with well marked hills and valleys, was far cleaner.

The scavengering and street cleaning were under the control of the Health Department. For this purpose the City was divided into five districts, the cleaning of each of which was let out to separate contractors. The contractor received in payment the street refuse, which he sold as manure, and about one thousand dollars in money. The streets received attention in proportion to their tendency to collect filth, but never more than twice a week, more usually once in two weeks. The numerous narrow alleys and courts, inhabited by the poor, and the depositories of garbage and worse, received little attention and were generally in a filthy condition. The most effective scavengering in these districts was done by swine which were allowed, although it was against the law, to roam through them at their pleasure. The copious showers which were frequent especially in summer, brought about the best results in street cleaning for the City. The streets were often of defective grade and in general roughly paved with cobblestones. There were storm-water gutters on each side, but as sewers were almost non-existent, there being only about two miles of storm-water sewers in the whole City, they led the water through and over streets directly into the Basin or into the nearest stream. With this storm-water went kitchen, bath, and laundry water and much garbage, as well as street manure and material from overflowing privies and cesspools. Between rains these streams were sluggish and in hot weather emitted offensive odors. The garbage and street sweepings

removed by the contractors were dumped on convenient vacant lots at the borders of the City until disposed of.

The night-soil from privies and cesspools was removed by licensed night-soil contractors and sold directly to farmers or manufactured into poudrette. At this time, a portion at least of the night-soil was deposited on the garbage and street manure dumps, and much of its was shipped out of the City on scows.

The nuisances from overflowing privies were a constant source of annoyance and danger to health.

In 1849, not more than one-half, and perhaps not more than one-third, of the population drank water from the public water supply derived from Jones' Falls; the remainder derived its water supply from springs and public and private wells. Many, if not most, of these last must have become grossly polluted by this time from the supersaturation of the subsoil from the numerous cesspools or from surface pollution from privies and overflowing cesspools. It is certain that the public water supply was at this date to some degree polluted from the settlements that grew up around the numerous mills dotting the course of Jones' Falls above the intake.

The better-to-do inhabitants, including the skilled laborers, lived in well built, single-family, brick houses. A considerable portion of the population, consisting mainly of recent immigrants and negroes, lived crowded together in small houses in narrow, dirty, ill-paved, and poorly drained alleys, with an inadequate water supply.

SEWERAGE

As previously indicated, at the time at which our period opens, there were no sanitary sewers in the proper sense of the term, and the underground drainage for storm water was very meagre. According to Wynne, in 1849, the aggregate of all the sewers did not exceed two miles in length. Previous to 1862, the few existing storm-water sewers had been put in in a haphazard way.

The first serious consideration of the sewerage question on the part of the City government was in 1859, when a Sewerage Commission was appointed, consisting of Henry Tyson, John Dukehart, and J. Mowton Sanders. In their report rendered in 1862, commonly called the Tyson Report, the Commissioners recommended the establishment of eight sewerage districts, in which sewers were to be built to carry off storm-water and household waste waters, exclusive of human excreta, more readily along the natural drainage lines. Jones' Falls, in which there was an awkward bend to the westward in the neighborhood of Saratoga and Lexington Streets, was to be straightened, and it was proposed that an intercepting storm-water sewer, running parallel to this stream, be built. Some of the recommendations of this Commission, including the straightening of Jones' Falls and the supporting of its walls with masonry, were carried out during the next few years, but no systematic record was kept of the dates and courses of many of the new sewers.

At the invitation of the city government, C. H. Latrobe, C. E., in 1881, made an extensive report on the sewerage question. Mr. Latrobe, recognizing that the subsoil had reached the limit of its capacity to care for human excreta by the cesspool and privy systems, recommended a plan for a dual sewerage system: one for surface water and rainfall, to discharge as before into the middle branch of the Patapsco (Spring Gardens), into the Basin, and into the Harbor; and the other for household waste and human excreta, to discharge partly into Middle River (the middle branch of the Patapsco) and partly into the lower harbor below Canton. Relatively very little was done in regard to the storm-water drains, and the recommendations for sanitary sewers were entirely passed over.

Between 1880 and 1890, the construction of storm-water sewers was continued in an irregular way, and Harford, Chatsworth, and Schroeder's Runs were covered over, but in the meantime, there had been a very considerable increase in the number of cesspools draining into the new and the old storm-water sewers which discharged into these runs, or Jones' Falls, or directly into the Basin and into the middle branch of the Patapsco. Many of the sewers, including these runs, were improperly trapped and gave off offensive odors. The uncovered Jones' Falls was, to a very great degree, a combined storm-water and sanitary sewer carrying so much filth that it was constantly necessary to dredge its lower portion for the removal of sediments of organic matter.

A second Sewerage Commission, under the chairmanship of Mr. Mendes Cohen, engaged Messers. Rudolph Hering and Samuel M. Gray as Consulting Engineers and Mr. Kenneth Allen as Assistant Engineer. After an exhaustive study, the Commission, in its report of 1896, recommended a dual sewerage system; the storm-water to be discharged as recommended before, and the domestic waste, including human excreta, to be disposed of by dilution into the deep waters of the Chesapeake Bay, well below the City. Of the two alternative methods proposed by the engineers, *i. e.*, chemical precipitation before such discharge and the use of filtration beds on land in Anne Arundel County, they objected to the former as unnecessary, and to the latter on account of its great expense.

The city government, fearing injury to the fishing industry, particularly on account of the danger of infecting oysters with typhoid bacilli, directed further investigation and a report on the best alternative plan. The Commission then suggested that the plan of land filtration be tried, but be restricted at first to the sewerage from the low level area, thus serving about one-third of the population. The whole matter was then dropped because the people refused to approve a bond issue to pay the cost of the work.

In 1905, the third Sewerage Commission was appointed. Messers. Hering, Gray, and Stearns served as a board of consulting engineers, and Mr. Calvin W. Hendrick was appointed Chief Engineer. Mr. Hendrick and his staff designed and superintended the building of a double system of sewers—surface water and sanitary—covering most of the built up sections of the City. The surface water sewers discharge the storm-water as before. The sanitary sewers carry domestic waste and human excreta to a point on Back River, to the

southeast of the City, where the sewerage is purified and the effluent discharged into the Bay. The system was completed in 1915. Connections were started on a limited scale in the fall of 1911 and were completed in 1917 and 1918. It was estimated by the Chief Engineer that the household sewerage of about 15,000 houses had been discharging into the Basin and Harbor. There are now over 90,000 houses connected, and in most of the old twenty-four wards, the privy and the cesspool have been eliminated. Thus, the opportunities for fly-borne typhoid must have been greatly restricted.

Much of the sanitary sewerage of a considerable district in the northwest and southwest sections of the City still finds its way into Gwynn's Falls, a stream already polluted with sewerage before it reaches the city limits. As the population so served is still relatively small and the stream is large and rapid, the insanitary conditions are by no means a nuisance comparable to those which obtained in Jones' Falls, or Harford, Chatsworth, and Schroeder's Runs in former days. Jones' Falls and its tributaries as well still receive a certain but relatively small amount of sanitary drainage from outlying sections of the city. The same may be said in regard to Herring Run, as it runs through the northeastern part of the City. This stream is already seriously polluted from sources to the north of the City. The closely built up Highlandtown, bounding the eastern margin of the City, still retains to a large degree the old, primitive method of storm-water and sanitary sewerage disposal which obtained in the old City before the construction of the new sewerage systems.

WATER SUPPLY

From its foundation until 1808, Baltimore depended upon the springs and wells within the City for its water supply, and perhaps to a certain extent, at its borders, upon the several streams. As early as 1792, the legislature gave permission to an insurance company to organize the Baltimore Water Company, with the privilege of supplying water to private users. The Company, however, did not avail itself of this privilege. In 1800, the legislature authorized the Mayor and City Council to introduce water into the City. On account of various delays on the part of the city government, on April 21, 1804, at a public meeting of citizens, a Committee, under the chairmanship of General Samuel Smith, and including John Eager Howard, was appointed to organize a stock company for this purpose. The Company was organized on May 24, 1804.

Jones' Falls having been chosen as the source of supply, a reservoir was constructed near what is now the southwest corner of Cathedral and Franklin Streets, and a wheel and pumps, located at the present site of the Calvert Street Station of the Northern Central Railroad Company, forced water from a common mill race on Jones' Falls, known as Keller's Dam which supplied Salisbury Mill, situated near the site of the old Belvedere Bridge, just east of the present Guilford Avenue Bridge. The main surface pipes were hemlock logs, with bores from 1-½ to 4 inches in diameter, joined by driving the spigot-shaped end of one log into the bell-shaped end of its mate. The joints were bound with wrought irons bands. The main valves were of cast iron with tapered spigot ends which were driven into the wooden mains, the valves being opened by lifting the valve plugs by means of hooks. The small surface pipes were cedar logs 6 inches in diameter with a 1 inch bore. The first iron pipes laid by the Water Company were imported from England about 1820. The Company supplied the city fire plugs and extended services to private dwellings as and when the revenue to be derived was sufficient to pay the cost and a profit. Service began in 1808. There were always comparatively large areas to which this water supply did not extend, or where it was not taken advantage of, and in which the water of springs and wells was used as in the earlier days.

Somewhat later, the Water Company erected a new pumping station near the old Belvedere Bridge and built an additional reservoir on the high ground at the northeast corner of the present Chase and Charles Streets and a third reservoir called the Mt. Royal Reservoir situated near the present Union Station of the Pennsylvania Railroad. This was supplied by natural flow with water from the mill-race of the Lanvale Cotton Company situated higher up on Jones' Falls. It will be noted that the Water Company did not undertake the construction of dams and large impounding reservoirs along the course of Jones' Falls, but obtained its water supply from the dams of industrial mills which dotted the course of the stream.

John Randel, Jr., in his report to the city government in 1836, recommended that the water be obtained from the Gunpowder River at Great Falls, that for this purpose a dam be built at Tyson's Mills and another across the Western Run, near York Pike, and that, with an aqueduct joining these two sources at Beaver Dam, water be led through the ridge of limestone rock and thence along the western slope of Jones' Falls Creek to a reservoir 300 feet above tide water near Baltimore.

According to Wynne, the service pipes to households, after 1820, were exclusively of lead. In 1849, he estimated that 5000 houses were supplied with hydrants. The City provided free hydrants in certain sections for the poor. At that time the average daily consumption of water was 500,000 to 1,000,000 gallons in the summer and much less in the winter. He describes the water as pure and soft and agreeable to the taste.

The City took over the Water Company in 1852, and after a sharp discussion as to whether the new water supply should be obtained from the Gunpowder River or from Jones' Falls, the contest was decided in favor of the latter. A dam was built at Relay House on the Northern Central Railroad, at an elevation of 220 feet above mean tide. From this, water was led by natural flow through an aqueduct four miles long to a high service reservoir in Hampden and thence by cast-iron pipes for distribution in the City and also to a low service reservoir at North Avenue and the Falls. This system was put into use in 1862. The impounding lake, now called Lake Roland, had an available capacity of 400,000,000 gallons.

The Hampden Reservoir had a storage capacity of 50,000,000 gallons, and the present Mt. Royal Reservoir had a capacity of 30,000,000 gallons.

In 1870, the present Druid Lake in Druid Hill Park, with a storage capacity of 429,000,000 gallons, was completed. Four years later the West High Service Reservoir in Druid Hill Park, with an elevation of 350 feet above mean tide was finished. This reservoir was designed to serve the rapidly growing western and northwestern sections of the City.

In 1862, the consumption of water was not over 8,000,000 gallons of water a day, and it was estimated that the new supply would furnish not under 20,000,000 gallons a day. On account of a severe drought in 1872, the City faced a water famine, and it became evident that the Jones' Falls water supply would have to be reinforced. For this reason, in 1874, a dam was constructed at Meredith's Ford on the Gunpowder River, and 5,000,000 gallons of water a day were forced through a main over the dividing ridge between the Gunpowder River and Jones' Falls into the Channel of Roland Run, a tributary of Jones' Falls, above Lake Roland.

The City then set to work to obtain the larger part of its water supply from the Gunpowder River. In 1875, the following extensive works were begun: An impounding reservoir on the Gunpowder River at Lock Raven with a capacity of 510,000,000 gallons and with a dam 800 feet long and 30 feet high; a gate-house; a supply tunnel 7 miles long, leading to a receiving reservoir at Lake Montebello with a storage capacity of 500,000,000 gallons; and a conduit a mile long from this lake to a gate-house at Clifton, whence a 40-inch main brought water to North Avenue.

The Gunpowder water was turned in direct to the city supply on September 28, 1881. In 1888 an additional storage lake, holding 265,000,000 gallons of water, was built at Clifton.

It would appear that after 1881, under ordinary conditions, at least seven-eighths of the city's water supply was derived from the Gunpowder River and not more than one-eighth from the old Lake Roland supply obtained from Jones' Falls. A comparatively small area in the southeastern portion of the City was supplied up until 1885 by the Baltimore Water and Electric Company.

In 1876, following a very severe and fatal outbreak of so-called typho-malarial fever, but which was probably paratyphoid, Health Commissioner Steuart employed Professor William P. Tonry to make chemical analyses of the water of suspected wells in this locality. The wells were found to be grossly polluted. In 1878 and 1879, Dr. Tonry again examined the water of a number of wells in different parts of the City and condemned a large proportion of them on account of pollution with organic matter. In 1885, he examined the waters of numerous wells in the City for the Commissioner of Health and condemned nearly all of them as grossly polluted. He also made chemical examinations of eight samples of mixed water from the Jones' Falls and Gunpowder River water supplies, taken from the city taps, and found them all suspicious. The Commissioners of Health, between this time and 1888, condemned a large number of springs and wells within the City and had them closed, so by the time of the annexation in 1888 there were comparatively few remaining wells in use within the then old city limits.

By the annexation of 1888, the City took over, especially on its northern boundary, a large territory rather thickly inhabited, the water supply of which was almost entirely derived from wells and springs. There was an almost complete absence of sewers of any kind in parts of this territory, especially in the Hampden-Woodberry district. In the first year of annexation, 15 cases of typhoid fever occurred in a locality in Woodberry in which the water supply was obtained from a single well. The city water supply was brought into this new territory, and the wells and springs were condemned and abandoned as rapidly as possible. As late as 1897, Dr. Stokes found on examination a large number of polluted wells in the Hampden-Woodberry district.

In 1892, Commissioner of Health McShane established a sanitary inspection of the Lake Roland watershed in order to reduce pollution of the water supply from this source, and in 1896 this inspection was extended to the Gunpowder watershed, and the pollution of these waters from the privies of private dwellings was, to a considerable degree at least, abated. In his report of this year, Commissioner McShane expressed the opinion that the general water supply was seriously polluted.

In this year the chemical and bacteriological laboratories were established in the Health Department, and from this date serious studies of the water supply have been made in both these laboratories.

In general it may be said that chemical and bacteriological examinations made in the Health Department, during this period, of the water of the Gunpowder River and of Jones' Falls and of certain of their larger tributaries, showed an increasingly high degree of pollution, indicated by the presence of organic material and high chlorine content, high colony counts, and the frequent presence of *B. coli;* that there were evidences, both from chemical and bacteriological standpoints, of pollution of the water impounded in the city's reservoirs; and that the water drawn from the city taps showed decided improvement over the reservoir water. In other words, the gross contamination of the water at its source was, to a considerable degree, modified by storage in the city's reservoirs. Dr. Stokes' reports show that there was a rather steady increase in pollution, as judged by the colon bacilli content of samples taken from city taps in 1897 to 1910, inclusive, from 4.5 per cent total samples in 1897 to 57.3 per cent total samples in 1910. He gives the average for the fifteen years, 1896 to 1910, inclusive, as 73.3 per cent of positive colon bacilli findings in 854 samples analyzed. The average bacterial count per cubic centimeter of the tap-water from 1896 to 1902, inclusive, was 600 bacteria. In 1907, it increased to 1300; in 1908, it had dropped back to 600; in 1910, the year of a very considerable typhoid fever epidemic, the average bacterial count per cubic centimeter was 544, and 57.3 per cent of 68 samples examined for colon bacilli were positive. In the previous year, 75 per cent of 112 such samples were positive.

It would appear that a considerable number of wells and springs were still in use in the City as late as 1910, for in this year Dr. Stokes reports the examination of 71 samples of such waters in which colon bacilli were demonstrated in 64.7 per cent.

In a valuable paper published in 1911 on *The Problem of Typhoid Fever in Baltimore,* Dr. W. W. Ford stated that he had examined samples of the Gunpowder River water, over a period of many years, and especially from October, 1910, to June, 1911, and had found high bacteria counts and demonstrated the presence of *B. coli* with great regularity. Ford was able to isolate *B. coli* in the majority of 1 c. c. samples, frequently in 0.1 c. c. and more rarely in 0.01 c. c. samples. He found that other intestinal organisms were also commonly present. The contamination of the water was especially marked in the dry weather of 1910.

As will be seen later, Dr. Jones had reached the conclusion in 1907 that the water must be responsible for at least the majority of typhoid fever cases in Baltimore. Dr. Stokes and Dr. Ford, in their studies of the situation reached the same conclusion in 1910 and 1911.

Purification of the city water supply, through the action of calcium hypochlorite, was begun in June, 1911. The hypochlorite was added to the water of both the Lake Roland and the Gunpowder River supplies at the gate chambers through

TABLE 1

THE LAKE ROLAND SYSTEM

		Average bacteria per c. c.	Percentage of bacterial reduction	Percentage of positive colon tests		
				0.1 c. c.	1 c. c.	10 c. c.
July	Raw water...	47,600	....	60	86	100
	Storage.....	725	99	26	57	84
	City taps....	4,410	91	0	22	64
August	Raw water...	38,540	....	76	..	..
	Storage.....	1,210	97	32	66	..
	City taps....	550	99	3	40	..
September	Raw water...	15,095	....	46	80	..
	Storage.....	286	98.5	4	31	..
	City taps....	170	99	6	30	..
October	Raw water...	17,830	....	91	100	..
	Storage.....	457	99.6	7	37	..
	City taps....	538	99.5	13	33	..
November	Raw water...	58,045	....	36	91	..
	Storage.....	627	98.9	0	19	..
	City taps....	1,430	97.6	4	26	..
December	Raw water...	6,540	....	20	35	..
	Storage.....	583	91	0	12	..
	City taps....	642	91.1	5	10	..

Available chlorine 0.4 parts per million during June and July; 0.6 parts per million during August; 0.75 during September to October 15; 1.0 from October 15 to December 31.

which the water passed from the impounding reservoirs to the city reservoirs. The addition of chlorine to the general water supply was followed by a marked diminution of the amount of bacterial pollution, as shown both by the bacterial counts and percentage of colon bacilli findings. In this year there was also a decided reduction in the typhoid morbidity and mortality in Baltimore. Stokes, Hachtel, and Freas studied exhaustively the effect of calcium hypochlorite upon the Baltimore water supply in 1911 and published a paper which is an important contribution to our knowledge on the subject (see Tables 1 and 2).

In 1910, the City began to carry out the plans of eminent engineers to increase the Gunpowder water supply by the

TABLE 2

THE LOCH RAVEN SYSTEM

		Average bacteria per c. c.	Percentage of bacterial reduction	Percentage of positive colon tests		
				1/10c.c.	1 c. c.	10 c. c.
July	Raw water...	60,800	....	62	88	100
	Storage.....	1,835	97	23	56	89
	City taps....	1,580	98	12	29	62
August	Raw water...	39,560	....	89	..	..
	Storage.....	2,497	94	14	48	..
	City taps....	134	99.5	11	37	..
September	Raw water...	12,409	....	74	..	..
	Storage.....	754	94.1	14	39	..
	City taps....	336	95.9	0	33	..
October	Raw water...	4,260	....	82	..	..
	Storage.....	638	98.6	13	39	..
	City taps....	596	99	2	33	..
November	Raw water...	129,996	....	55	..	..
	Storage.....	1,227	99.1	7	20	..
	City taps....	1,085	99.2	8	38	..
December	Raw water...	19,313	....	29	92	..
	Storage.....	1,916	90.1	5	22	..
	City taps....	1,227	93.7	0	12	..

Available chlorine 0.4 parts per million during June and July; 0.6 parts per million during August; 0.75 during September to October 15; 1.0 from October 15 to December 31.

erection of a higher dam and the creation of a larger impounding reservoir at Lock Raven and to purify this supply by appropriate filters established near the Montebello Reservoir. This work was completed and the filtration plant put into operation on September 15, 1915. At this date, too, the Lake Roland water supply was abandoned, though the works are retained for use in case of emergency. For a few weeks in the winters of 1916 and 1917, on account of necessary repairs to a tunnel, this supply, after heavy chlorinization, was used. For at least two years after the new water supply became available, studies in the bacteriological laboratories showed that frequently colon bacilli were present in the water from city taps in 10 c. c. samples, and not infrequently in samples of even 1 or 0.1 c. c. In some months, over 25 per cent of the 10 c. c. samples of tap-water showed the presence of *B. coli.* These findings in the tap-water were often, indeed almost constantly, at variance with the results of the bacteriologist at the water-works. In the last two years, the colon bacillus determinations, obtained in the City Bacteriological Laboratory, have been relatively low. If low colony counts and low percentage of colon bacillus findings mean water free from typhoid bacilli, it is difficult to see that the water can now play any large part as a bearer of typhoid bacilli in the old twenty-four wards of the City. It seems clear that since the

beginning of the use of chlorine purification in 1911, the water supply has become a decreasingly important source of typhoid infection in these wards. Valuable aids to filtration in guarding the city water supply from infection of typhoid bacilli are inspections of the watersheds by the Water Department and the cooperation of the State Board of Health in notifying the Water Department of the presence of reported cases of typhoid fever on the watersheds and in taking appropriate measures to prevent the pollution from them. The map of these two watersheds, separated by a ridge of hills, shows both to be the seat of numerous larger and smaller settlements, many of them villages of considerable size. Inspection shows that many of the smaller, and all of the larger, tributary streams serve as sewers of direct discharge for human excreta from villages, small settlements, and isolated houses and institutions, and that human waste from many dwellings reaches them indirectly from pipes or surface washing. There are a great number of stables for horses and cattle, as well as pigstyes, on their banks, and many stableyards and paddocks straddle the smaller streams. While a great deal has been done in the last few years by the State Board of Health to enforce measures which have decreased the pollution from the larger settlements, it is evident to any thoughtful observer that, unless some unforseeable revolution occurs in the methods of disposal of human waste, it is hopeless to expect that in any reasonably near time the water from either of these sheds will be safe for drinking purposes without treatment.

PAVING AND STREET CLEANING

As early as 1782, grading and paving of the streets and sidewalks was undertaken in a systematic manner, under a special commission appointed by Act of the General Assembly. The work was energetically carried out. The street pavements, at first confined to the business section, were of rough cobblestones, and this character of pavement was in general use until 1911, except where Belgian blocks and occasionally asphalt were substituted on a few business streets and prominent thoroughfares. The report of the City Engineer in that year showed the following street mileage of each material: cobblestone, 354.82; Belgian block, 43.49; sheet asphalt, 19.23; vitrified brick, 19.15; wooden block, 1.63; ordinary macadam, 56.01; bituminous macadam, 2.73; bitulithic, 10.10; cement surface, 2.01; unpaved, 57.73. Much of the better paving had been done in connection with the rebuilding of the section of the City burned in the great fire of 1904.

Since 1912, under the stimulus of Mayor James H. Preston and following the building of the new severage system, many miles of streets have been regraded to facilitate surface drainage and paved with smooth pavements. Following this, the greater part of the private alleys, which since the early history of the City had been unpaved or paved with cobblestones and were so rough and irregular as to render drainage and cleaning almost impossible, was brought to proper grade and smoothly paved with substantial material. But for the war, this work would have been completed in most of the old twenty-four wards in 1918.

In the meantime, the Street Cleaning Department had been increased in personnel, equipment, and efficiency for the cleaning of streets and alleys and the prompt removal of garbage. As a result of all these improvements and the practical elimination of the cow stables within the City and the substitution, to a great extent, of the automobile for the horse, the stable and the house fly have been greatly diminished in numbers.

MILK AND OTHER FOODS

As in other cities, so in Baltimore, in the early stages of growth, the milk supply was obtained from cows kept in stables and on lots within the city limits. With growth, the neighboring and later, especially with the development of railroads, the distant suburbs were called upon. Speaking by and large, as a natural product, the city and nearby milk were probably of better quality than that from a distance. With city growth and crowding, the feeding of garbage and distillery slop to cows, and the many and rapidly increasing chances of contamination with the microorganisms causing diseases in man, and notably those concerned with diseases of the alimentary tract, especially typhoid fever and dysentery, the city produced milk became not only poorer in quality, but more and more dangerous.

The first recorded investigation of Baltimore's milk is that of Professor Tonry, made at the instance of the Commissioner of Health in 1873. He showed that the best milk came from "dry fed" cows in good stables within the City and immediate suburbs; next stood the farm milk brought in by railroads; and lastly, the milk of the badly stabled, sickly, slop fed cows within the City. Evidence of watering of milk was convincing.

In 1879 an ordinance on milk was passed, making it unlawful to mix water, or any drug, or other article, with milk offered for sale, but there was no provision for its enforcement.

In spite of the recommendations of the Health Department, especially in 1887, when attention was called by the Assistant Commissioner, Dr. McShane, to the milk epidemics of typhoid fever, tabulated by Ernest Hart, no steps were taken by the city authorities to give the Health Department power to control the milk supply until 1894. Soon after the passage by the legislature of an act granting the necessary power, the Mayor and City Council passed an ordinance on May 15, 1894, providing for the inspection of milk and other foods and authorizing the appointment of a chemist and three inspectors. According to the milk standards set by this ordinance, there could be sold in Baltimore only pure, unadulterated, unsophisticated milk, the natural product of healthy cows, not deprived of any part of its cream, and to which no additional liquid or solid or preservative had been added, and which at 60° Fahr. shall have a specific gravity of not less than 1029, total solids, 12 per cent, and butter fat, 3 per cent.

In 1896 an ordinance regulated the ventilation, flooring, and cleanliness of cow stables; required the tuberculin test for milch cattle within the City; and made compulsory the prompt reporting to the Health Department not only of the occurrence of "contagious and infectious" diseases among

cows, but of cases of asiatic cholera, croup and diphtheria, measles, scarlatina, smallpox, typhus and typhoid fevers upon premises with milch cows, or where milk is handled or offered for sale. Milk from premises with cases of any of these or other infectious diseases could not be sold or given away until the Commissioner of Health deemed it safe. Persons connected with dairying and milk handling were forbidden to enter such premises.

By the ordinance of 1902, the sanitary standards under which milch cattle could be kept were made more stringent by requiring non-absorbent floors in stables, with proper drainage and more air space and range for cows, and by forbidding privies, cesspools, and the presence of fowl, swine and horses in stables or connected with rooms where milk and cream were handled.

In 1908, a very sweeping milk ordinance was passed, giving the Health Department complete control over the milk supply, requiring permits for handling milk, dairy farm inspection, the sterilization of utensils, regulation of conditions under which milk could be sold, excluding for sale the milk of slop fed cows, and raising the standard for total solids to 12½ per cent and of butter fat to 3½ per cent. In all respects except one it was a model ordinance, and during the next few years a far-reaching scheme for the sanitary control of milk was put into operation. The weak point of the ordinance lay in its general terms. The regulations made by the Department, especially in regard to sanitary conditions under which milk was handled, sold, and pasteurized, were often successfully contested by certain types of milk dealers as unreasonable, and the Department, which was well and intelligently organized for the purpose, was continuously held up in important details by suits brought to restrain its actions. Conditions, especially in regard to the relation of milk to the spread of communicable disease, were undoubtedly greatly improved. Those concerned in the administration of this ordinance deserve high praise.

Between 1908 and 1916, great changes took place in the milk business, especially in regard to the proportion of milk pasteurized and the attitude of the dealers to the milk problem. In 1917, there was passed an amending ordinance regulating specifically and in detail the important points of administration found impossible of execution under the more general ordinance of 1908. The ordinance of 1917 was passed as drawn by a committee headed by Dr. William H. Welch, and though put into execution under conditions of great disadvantage, it has finally met the best hopes of its authors. It is within the bounds of accuracy to state that all the milk used in the City is reasonably safe from typhoid infection. The great bulk of the milk is pasteurized with fair efficiency, put into bottles or other containers well washed, and, on the whole, if not absolutely sterilized, fairly safe from typhoid infection. The small quantity of raw milk of special grades allowed to be sold has stood the test of experiment without transmitting typhoid fever, and there is every reason for concluding that it is effectually safeguarded. In 1918 and in 1919, no cases of typhoid fever were traced to milk. Certainly there were no ascertainable milk outbreaks such as so often occurred in previous years.

The new milk ordinance did not go into effect until November, 1917, and, on account of war conditions, it was not possible for many dealers to secure and install pasteurizing and other apparatus until well into 1918. Labor for working the plants and ice for refrigeration were also difficult to obtain. It was not until 1919, therefore, that the real advantage of the administration of the ordinance, as shown in the reduction in bacterial counts of the milk supply, was gained. The results for pasteurized milk as delivered from street wagons are illustrated in Table 3 and in the following figures, expressed in terms of annual Levy rating of bacteria per cubic centimeter for the total milk supply: 1917, 500,000 (1959 samples); 1918, 600,000 (2741 samples); 1919, 67,000 (3899 samples).

TABLE 3

LEVY AVERAGE OF NUMBERS OF BACTERIA PER C. C. IN SAMPLES OF PASTEURIZED MILK (ABOUT 300 MONTHLY) COLLECTED FROM WAGONS ON THE STREET

Month	Levy average of numbers of bacteria per c.c.		
	1918	1919	1920
January	282,000	56,000	13,000
February	475,000	41,000	8,300
March	450,000	54,000	15,000
April	650,000	52,000	.....
May	1,500,000	96,000	.....
June	1,200,000	130,000	.....
July	1,500,000	120,000	.....
August	1,700,000	110,000	.....
September	840,000	120,000	.....
October	350,000	74,000	.....
November	115,000	14,000	.....
December	71,000	27,000	.....

Judging from the grossly insanitary conditions under which milk was produced and sold in Baltimore from the earliest times and from the number of milk outbreaks recorded in the reports of the Health Department, it is certain that this article of food has until recently played a very important rôle in the spread of typhoid fever in Baltimore. It is likely that the interference with the watering of milk which attended the enforcement of the ordinance of 1894 was, to a considerable degree at least, responsible for the fall in the typhoid rate during the next few years. It was not, however, until the enforcement of the new ordinance of 1917 that milk, as a vehicle of infection for typhoid fever, was practically eliminated.

Of the other foods than milk, butter, cheese, shell-fish, and vegetables and fruits eaten raw are the only ones of importance, from the practical standpoint, in regard to possibility of carrying typhoid fever infection. Control of these by the Health Department has been limited to preventing those sick with typhoid fever, those attendant upon them, and known carriers from handling food or selling or giving it to others.

No outbreaks of typhoid fever spread by any of these substances have ever been convincingly traced by the officials of

the Health Department, but it is quite probable that by some of these means, notably butter and shell-fish, especially oysters, typhoid infection has been carried here. Instances of the spread of typhoid fever in a large city, in either isolated cases or in epidemic outbreaks, by means of butter, cheese, and vegetables, would in the nature of the case be hit upon only by chance. Vegetables grown on ground fertilized by night-soil were sold in Baltimore for many years and perhaps are now, but there are no observations upon the relation of this circumstance to the spread of typhoid fever in the community. The finding of *B. coli* on such vegetables means nothing in this relation, for it would be strange if this organism were not present on the surface of all vegetables exposed to the soil and not protected by pods like peas and beans. Oysters from polluted waters have undoubtedly been sold in Baltimore and typhoid fever may well have been spread by this means in years past; but the height of typhoid prevalence has not synchronized with the oyster season since 1881.

STUDY OF TYPHOID FEVER IN THE HEALTH DEPARTMENT

It now becomes our task to consider, as fully as may be, the studies on typhoid fever made in the Health Department.

The first mention of the etiology of typhoid fever in the Health Department reports occurs in 1875 when Commissioner Stewart attributed this disease and certain others to sewer gas entering houses from imperfectly trapped sewer wells, just as Thomas H. Buckler, in 1851, had blamed the cholera and typhoid fever at the Almshouse on the foul gas of an open cesspool. In 1876, Commissioner Stewart attributed an outbreak of "typho-malarial fever" at Fell's Point to polluted wells and had them closed. Three years later, he ascribed the typhoid fever occurring along Harford Run to the foul condition of that sewer stream. Again, in 1880, he blamed the disease on sewer gas, after his inspectors, who had been sent to visit all houses harboring fatal cases of typhoid fever, reported that they had invariably found full or overflowing privy wells or faulty water closets. As a result of this conclusion, very generally accepted at the time, Dr. Stewart got plumbing inspection established in 1885. In the meantime he had bent every effort to control the nuisance involved in the removal of night-soil. At this time, too, he started routine chemical examinations of the waters of springs and wells, a number of which he had condemned. He also began to question the safety of the general water supply. In 1888, Dr. Stewart closed many wells in the Hampden-Woodberry district of the newly annexed territory on account of pollution, having traced 15 cases of typhoid fever in this district to one well.

Dr. George H. Rohe, in his report for 1890, gave more information concerning typhoid fever in Baltimore than all previous Health Commissioners. After noting the progressively increasing number of deaths during the previous nine years, he pointed out that the great excess of cases in the twenty-first and twenty-second wards was due to the polluted wells in the newly annexed territory and further stated that the sanitary inspectors reported that many residents contracted the disease out of the City, particularly at health resorts, and that many non-residents were brought into the City to the hospitals for treatment. The truth of the last statement can be vouched for by all who were associated with Baltimore hospitals at that time.

In 1894, typhoid fever together with certain other diseases was made reportable to the Health Department.

Commissioner McShane, in his report for 1895, devoted considerable space to typhoid fever. He recognized that the disease is not contagious in the usual strict sense of the term, but certainly commonly communicated through infected foods and drinks. He recommended that every precaution should be taken to guard the water supply. In this year, the City Chemist attributed 12 cases of typhoid fever in an institution to infected milk, and the epidemic subsided after the milk supply was changed. Dr. McShane also took steps to stop the handling of milk by persons associated with cases of typhoid fever and the sale of milk from premises harboring cases of this disease. He stated in 1897 that, "60 per cent of the cases of typhoid fever, concerning which an intelligent history could be gotten, were infected outside of the City."

In 1899, Commissioner Jones made the first spot map, giving the location of reported cases of typhoid fever and showing that the disease was rather evenly distributed over the City. This point was illustrated in his maps for 1902 and succeeding years. In 1899 and in other years, particularly in his elaborate study of 1907, Dr. Jones reached the conclusion that though flies and milk did play a part in spreading typhoid fever, they could not explain the bulk of the cases for obvious reasons, for too many cases occurred in the months without flies and the cases, in the average years, were too well scattered to be explained satisfactorily by milk infection. He was alive to the importance of this latter means of transmission, however, and recorded three striking milk epidemics: one in 1903 among the workers of a large factory who drank milk supplied to them at luncheon (there were 26 cases with 4 deaths); a second in 1906, an extensive epidemic in the Hampden-Woodberry district; and a third in 1907, a small epidemic of 19 cases.

Contact infection as evidenced by secondary cases in households fell far short, of course, of explaining the great annual visitation. From Dr. Jones' figures, I estimate that in the years, 1904, 1905, 1906, and 1907, somewhere between 7 and 9 per cent of the cases could be classed under this category. Of 2225 cases investigated from the standpoint of out-of-town infection, it was found that 489, or only approximately 22 per cent of the cases had been out of the City. Therefore, nearly four-fifths of the cases could not have received their infections outside of the City. On the other hand, there were still many polluted wells within the City, especially in certain parts, and chemical and bacteriological examinations of the general water supply year by year showed increasing evidences of pollution, in spite of sanitary inspections and nuisance abatements along the watersheds. Dr. Jones concluded that the water was the means through which the bulk of the City's typhoid was spread.

Dr. Jones insisted that there were actually many more cases of typhoid fever in the City than were reported. He estimated that in 1906 and 1907, there must have been between 2000 and 2500, instead of the 1000 to 1400 reported. This was based upon the fact that the number of reported deaths calculated on a 10 per cent fatality basis would give these totals. For instance, in 1907 there were 1420 reported cases and 230 deaths, a case fatality rate of 16.3 per cent; on a 10 per cent fatality basis there should have been 2300 reported cases.

This study of typhoid fever by Dr. Jones in the report of 1907 will always stand out as one of the best pieces of work done in the Baltimore Health Department. The task he set himself was to determine the manner in which the bulk of the typhoid infection took place at that date. Recognizing that there were many sub-sources, important enough in themselves, Dr. Jones after careful and judicious weighing of the available evidence, came to the conclusion by orderly exclusion that typhoid fever in Baltimore was at that time chiefly water-borne. Important evidence in support of this conclusion had been accumulated during the preceding years by the chemist, Dr. Lehmann, and the bacteriologist, Dr. Stokes. For the next three years from 1908 to 1910, Dr. Jones exerted himself on the administrative side, as the records show, to eliminate as much as possible the spread of typhoid fever by subsidiary channels; *i. e.*, household contact, flies, and milk.

If there were space, I should like to point out in detail the value of the studies of Dr. Stokes on the water, particularly in connection with the effects of chlorinization and filtration, and the important part he has taken in the whole question of the water supply. Attention should likewise be called to the study of the milk supply and the well directed administration of the details of its control by Drs. Blanck and Hopkins and their assistants in later years, as well as the pioneer work of Drs. Lehmann and Hoffmann, their predecessors. Dr. Jones left the Baltimore Health Department in the fall of 1915, and took charge of the Bureau of Communicable Diseases of the State Health Department. Here in various ways, particularly in tracing cases reported in Baltimore to sources of infection in the counties of Maryland, and in following up clues, in removing cases from the Baltimore list and crediting them to counties of origin, and vice versa, as determined by the evidence, he continued to play an important rôle in the study of typhoid fever in the City.

Dr. W. W. Ford, in his independent investigations of the milk and water supplies and analysis of the Health Department records of the reported cases and deaths of typhoid fever, confirmed the conclusions of Dr. Jones and Dr. Stokes, and thereby rendered an important public service at a critical time when both the public and the medical profession were apathetic.

In 1909, the mortality rate per 100,000 fell to about 24, the lowest in the recorded history of the City, but in 1910, it jumped to over 42, about the level of 1907. As I have already stated, the treatment of the water with hypochlorite of lime and later with alum in addition was begun in June, 1911, and the typhoid rate again dropped abruptly in 1911 and 1912. Since this period there has been a continuous fall in the rate to the present level (in the old city wards).

But it must be pointed out at the same time, that during this period from 1911 to 1919, other factors besides purification of water by chlorinization and filtration have come strongly into play. First in importance perhaps is the doing away with great numbers of privies, a considerable administrative feat on the part of the Health Department, by forcing connections with the new sanitary sewerage system; second, efforts on the part of the Health Department to restrain fly-borne typhoid; third, progress in curbing infection through milk; fourth, education of the public, and to some degree at least, anti-typhoid vaccination; and last, the decline of typhoid in the rural districts, due very largely to the increasing activities of the State Health Department.*

* To be continued in the September Bulletin.

A STUDY OF THE INVALID REACTION[1]

By Esther Loring Richards

(From the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital)

No class of patients inflicts so much strain on the time, patience and medical wisdom of the general practitioner and the specialist as hypochondriacs; and no class of patients suffers more at the hands of the profession than do these unfortunate members of society. The helplessness of efforts to serve this body of ailing human beings seems due to a persistence in our thinking of what Adolf Meyer has called "the medically useless contrast of mental and physical."

According to the pioneers in "neurasthenia" there was a physical basis not only for all its somatic symptoms, but also for its "psychic" manifestations which were elastic enough to include every reaction except outspoken major psychoses and organic brain disease. This physical basis was faulty nutrition of the nerve cells with resulting increased fatigability of the nerves *per se*. Later Janet and Freud invented ingenious psychological explanations to account for the "psychic" expressions of "neurasthenia."

In studying the 60 cases of invalidism presented in this paper the writer has had but one idea, and that is to approach each case as a problem by itself, to describe faithfully the facts which it presents, and to study them for the purpose of ascertaining what they mean in the patient's life; in

[1] Abstract from the Archives of Neurology and Psychiatry, 1919, II, No. 4, October, 1919.

what setting of life experiences and constitutional make-up, as well as biological activities, they occur; what opportunities for modification they offer, not only from the standpoint of the individual's metabolism and hygiene, but also from that of his constructive constitutional assets, his adaptive resources, his material for instinctive readjustments. With this aim in view it becomes useless to haggle over what symptoms should be charged up to mind and what symptoms to body.

Fifteen of the 60 patients refused to remain for treatment when told that their exclusive salvation did not lie in a continuance of drug and operative therapy. Of the 45 patients treated 16 were discharged as "well" and have remained so; 25 were discharged as "improved," and four as "unimproved." It was not possible to trace 11 of the "improved," but of the remaining 14, six are completely well, four are back at work in spite of a few complaints, and four have relapsed into their former invalidism. As to the "unimproved," two are well, one is at another hospital, and one cannot be traced. The ages of the group vary from 20 to 72 years. The proportion of females to males is 3 to 1. The average duration of symptoms is 5 years; the average length of their stay in the clinic is 12 weeks.

Symptoms.—Their complaints included headache, dizziness, general weakness, nausea, eructation, insomnia, anorexia, etc.

Examination.—Every patient was subjected to routine examinations as follows: A general physical examination including a neurological status, an examination of the reproductive apparatus, together with laboratory studies of the urine, blood, etc. These inquiries were supplemented by consultations with other hospital clinics such as the dental, Roentgen ray, electrocardiographic, etc., and by such special investigations as gastric analyses, blood-sugar determinations, blood cultures, etc., according as the facts of the routine examinations or the patient's complaints indicated further research. The psychopathologic data were derived from a record of the individual's mental status, and a study of the facts of his growth and development from childhood with particular emphasis on the constitutional make-up and reaction tendencies.

Method of Treatment.—The patient was given a frank report of the various examinations, and invited to think of his incapacitations, not as a disturbance in functionating of some point of visceral strategy from which his symptoms seemed falsely to emanate, but to think of his symptoms as substitutes for reactions to unhappy experiences, thwarted ambitions, petty jealousies, romantic disappointments, an empty and dissatisfied life, a desire to escape marital or domestic responsibilities, etc. Along with education in this concept he was given the benefit of any hygienic lifts suggested by the various examinations, such as attention to the weight curve, hemoglobin, eyestrain, etc. Combined with the physician's conscientious survey of the facts of each case was a ward routine arranged so that the patient got a full and well-ordered day with gymnasium, occupation class, recreation, and leisure for reading, writing letters, etc. It has been found that these concrete activities not only form a sort of natural bridge between the self-limitations of the invalidism and the return to normal action and interests toward which the patient is headed, but they also restore confidence in his somatic capabilities in general, and especially in certain viscera against which he has so long nursed suspicions of incompetence. He learns that he can eat proteins, carbohydrates and fats without disaster, that he can use his eyes without headaches; and can exercise without fatigue.

No. 18 was a single woman of 33 who since 1904 had suffered from diffuse headaches accompanied by nausea, vomiting, and frequently "falling spells" without loss of consciousness. In 1911 she had to give up work and from that time on had lived the life of a recluse. She had been treated for epilepsy without improvement. On admission the physical, neurological and laboratory examinations were negative.

The patient had been a bed-wetter till 6 years, and was a timid, self-conscious child. She had a narrow, rigid home environment where every normal instinct for recreation, social outlets and the expression of her individuality was repressed by a domineering mother. She reacted to this atmosphere with a feeling of inferiority. She shrank from meeting people, feared to take responsibility and suppressed all interest in the opposite sex. At first headaches and "falling spells" followed some exceptional physical or emotional strain, but from 1910 they occurred irrespective of any unusual event, seeming to represent her only means of getting square with an intolerable home situation.

In discussing matters with her the patient was told that her complaints were the expression of her inner conflicts and dissatisfactions, and that the solicitude and sympathy called forth by her affliction satisfied her natural craving for affection and the expression of her individuality. She was urged to reach out toward new outlets in the cultivation of friends, social interests, recreation and occupation. Since discharge three years ago the patient has had no "falling spells," and but seven or eight headaches a year, none of which have been severe enough to keep her from working eight hours a day.

PUBLICATIONS

The following nine monographs:

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. WINTERNITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, $2.00.

Leukaemia of the Fowl. Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D. Price $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. VAN DER STRICHT and T. WINGATE TODD. Price, $2.00.

The Operative Story of Goitre. The Author's Operation. By WILLIAM S. HALSTED, M. D. Price, $3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By CURLE L. CHALLANDER, M. D. Price, $2.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

THE JOHNS HOPKINS HOSPITAL REPORTS

VOLUME I. 483 pages, 99 plates.

VOLUME II. 570 pages, with 38 plates and figures.

VOLUME III. 766 pages, with 69 plates and figures.

VOLUME IV. 504 pages, 33 charts and illustrations.

VOLUME V. 480 pages, with 32 charts and illustrations.

The Malarial Fevers of Baltimore. By W. S. THAYER, M. D., and J. HEWETSON, M. D.
A Study of some Fatal Cases of Malaria. By LEWELLYS F. BARKER, M. B.

Studies in Typhoid Fever.

By WILLIAM OSLER, M. D., with additional papers by G. BLUMER, M. D., SIMON FLEXNER, M. D., WALTER REED, M. D., and H. C. PARSONS, M. D.

VOLUME VI. 414 pages, with 79 plates and figures.

VOLUME VII. 537 pages with illustrations.

VOLUME VIII. 552 pages with illustrations.

VOLUME IX. 1060 pages, 66 plates and 210 other illustrations.

Contributions to the Science of Medicine.

Dedicated by his Pupils to WILLIAM HENRY WELCH, on the twenty-fifth anniversary of his Doctorate. This volume contains 38 separate papers.

VOLUME X. 516 pages, 12 plates and 25 charts.

VOLUME XI. 555 pages, with 38 charts and illustrations.

VOLUME XII. 548 pages, 12 plates and other illustrations.

VOLUME XIII. 605 pages, with 6 plates, 201 figures, and 1 colored chart.

VOLUME XIV. 632 pages, with 97 figures.

Studies in Genito-Urinary Surgery.

The Treatment of Prostatic Hypertrophy by Conservative Perineal Prostatectomy. An analysis of cases and results based on a detailed report of 145 cases. By HUGH H. YOUNG, M. D.
Recto-Urethral Fistulæ. Description of New Procedures for their Prevention and Cure. By HUGH H. YOUNG, M. D.
The Early Diagnosis and Radical Cure of Carcinoma of the Prostate, being a study of 40 cases and presentation of a radical operation which was carried out in four cases. By HUGH H. YOUNG, M. D.

VOLUME XV. 542 pages, with 87 illustrations.

Twelve papers on pneumonia. By DRS. CHATARD, FABYAN, EMERSON, MARSHALL, MCCRAE, STEINER, HOWARD and HANES.
A Study of Diarrhœa in Children. J. H. MASON KNOX, JR., M. D., and EDWIN H. SCHORER, M. D.
Skin Transplantation. By JOHN STAIGE DAVIS, M. D.
Epidemic Cerebrospinal Meningitis and Serum Therapy at The Johns Hopkins Hospital. By FRANK J. SLADEN, M. D.

VOLUME XVI. 670 pages with 151 figures.

Studies in the Experimental Production of Tuberculosis in the Genito-Urinary Organs. By GEORGE WALKER, M. D.
The Effect on Breeding of the Removal of the Prostate Gland or of the Vesiculæ Seminales, or of Both; together with Observations on the Condition of the Testes after such Operations on White Rats. By GEORGE WALKER, M. D.
Scalping Accidents. By JOHN STAIGE DAVIS, M. D.
Obstruction of the Inferior Vena Cava with a Report of Eighteen Cases. By J. HALL PLEASANTS, M. D.
Physiological and Pharmacological Studies on Cardiac Tonicity in Mammals. By PERCIVAL DOUGLAS CAMERON, M. D.

VOLUME XVII. 586 pages with 21 plates and 136 figures.

Free Thrombi and Ball Thrombi in the Heart. By JOSEPH H. HEWITT, M. D.
Bensol as a Leucotoxin. By LAWRENCE SELLING, M. D.
Primary Carcinoma of the Liver. By MILTON C. WINTERNITZ, M. D.
The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL. D., F. S. S.
The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN, M. D.
The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D.
Venous Thrombosis During Myocardial Insufficiency. By FRANK J. SLADEN, M. D., and MILTON C. WINTERNITZ, M. D.
Leukæmia of the Fowl: Spontaneous and Experimental. By HARRY C. SCHMEISSER, M. D.

VOLUME XVIII. 445 pages with 124 figures.

Fasciculus I.

A Study of a Toxic Substance of the Pancreas. By E. W. GOODPASTURE, M. D., and GEORGE CLARK, M. D.
Old Age in Relation to Cell-overgrowth and Cancer. By E. W. GOODPASTURE, M. D., and G. B. WISLOCKI, M. D.
The Effect of Removal of the Spleen Upon Metabolism in Dogs; Preliminary Report. By J. H. KING, M. D.
The Effect of Removal of the Spleen Upon Blood Transfusion. By J. H. KING, M. D., B. M. BERNHEIM, M. D., and A. T. JONES, M. D.
Studies on Parathyroid Tetany. By D. WRIGHT WILSON, M. D., THORNTON STEARNS, M. D., J. H. JANNEY, JR., M. D., and MADGE DEG. THURLOW, M. D.
Some Observations on the Effect of Feeding Glands of Internal Secretion to Chicks. By M. C. WINTERNITZ, M. D.
Spontaneous and Experimental Leukæmia in the Fowl. By H. C. SCHMEISSER, M. D.
Studies on the Relation of Fowl Typhoid to Leukæmia of the Fowl. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.
Hyaline Degeneration of the Islands of Langerhans in Pancreatic Diabetes. By M. C. WINTERNITZ, M. D.
Generalized Miliary Tuberculosis Resulting from Extension of a Tubercular Pericarditis Into the Right Auricle. By M. C. WINTERNITZ, M. D.
Acute Suppurative Hypophysitis as a Complication of Purulent Sphenoidal Sinusitis. By T. R. BOGGS, M. D., and M. C. WINTERNITZ, M. D.
A Case of Pulmonary Monilíasis in the United States. By T. R. BOGGS, M. D., and M. C. PINCOFFS, M. D.
Gaucher's Disease (A Report of Two Cases in Infancy). By J. H. M. KNOX, M. D., H. R. WAHL, M. D., and H. C. SCHMEISSER, M. D.
A Fatal Case of Multiple Primary Carcinomata. By E. D. PLASS, M. D.
Congenital Obliteration of the Bile-ducts. By JAMES B. HOLMES, M. D.
Multiple Abscesses of the Brain in Infancy. By JAMES B. HOLMES, M. D.
Gastric Cancer in a Woman of Twenty-six Years. By R. G. HUSSEY, M. D.
Subdiaphragmatic Abscess with Rupture Into the Peritoneal Cavity Following Induced Pneumothorax for Pulmonary Hæmorrhage. By R. G. HUSSEY, M. D.
Heart Block Caused by Gumma of the Septum. By E. W. BRIDGEMAN, M. D., and H. C. SCHMEISSER, M. D.
Analysis of Autopsy Records.
A. The Johns Hopkins Hospital. (Table Showing Percentage of Autopsies.)
B. The City Hospitals, Bay View. (Table Showing Percentage of Autopsies.)
"The Monday Conferences."
Clinical Representatives on the Staff of the Department of Pathology.
Donation.

Fasciculus II.

The Rôle of the Autopsy in the Medicine of To-day. By M. C. WINTERNITZ, M. D.
Experimental Nephropathy in the Dog. Lesions Produced by Injection of *B. bronchisepticus* into the Renal Artery. By M. C. WINTERNITZ, M. D., and WILLIAM C. QUINBY, M. D.
Mesarteritis of the Pulmonary Artery. By M. C. WINTERNITZ, M. D., and H. C. SCHMEISSER, M. D.
A Clinical and Pathological Study of Two Cases of Miliary Tuberculosis of the Choroid. By ROBERT L. RANDOLPH, M. D., and H. C. SCHMEISSER, M. D.
The Blood-vessels of the Heart Valves. By STANHOPE BAYNE-JONES, M. D.
Equilibria in Precipitin Reactions. By STANHOPE BAYNE-JONES, M. D.
Carcinoma of the Pleura with Hypertrophic Osteoarthropathy. Report of a Case with a Description of the Histology of the Bone Lesion. By STANHOPE BAYNE-JONES, M. D.
The Interrelation of the Surviving Heart and Pancreas of the Dog in Sugar Metabolism. By ADMONT H. CLARK, M. D.
Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula Associated with Fused Kidney. A Case Report and A Summary of the Literature on Congenital Anomalies of the Esophagus. By E. D. PLASS, M. D.
Ectopia Cordis, with a Report of a Case in a Fifteen-Month-Old Infant. By JAMES B. HOLMES, M. D.
Studies in the Mechanism of Absorption from the Colon. By SAMUEL GOLDSCHMIDT, M. D., and A. B. DAYTON, M. D.
Report of Two Fatal Cases Following Percy's Low Heat Treatment of Carcinoma of the Uterus. By V. N. LEONARD, M. D., and A. B. DAYTON, M. D.
The Relationship in Typhoid Between Splenic Infarcts and Peritonitis Unassociated with Intestinal Perforation. By A. B. DAYTON, M. D.
Left Duodenal Hernia. By A. B. DAYTON, M. D.
Histological as Related to Physiological and Chemical Differences in Certain Muscles of the Cat. By H. HAYS BULLARD, M. D.
A Method of Clearing Frozen Sections. By H. HAYS BULLARD, M. D.
On the Occurrence and Significance of Fat in the Muscle Fibers of the Atrio-Ventricular System. By H. HAYS BULLARD, M. D.
Studies on the Metabolism of Cells *in vitro*. I. The Toxicity of α-Amino-Acids for Embyonic Chicken Cells. By MONTROSE T. BURROWS, M. D., and CLARENCE A. NEYMANN, M. D.
The Significance of the Lunula of the Nail. By MONTROSE T. BURROWS, M. D.
The Oxygen Pressure Necessary for Tissue Activity. By MONTROSE T. BURROWS, M. D.
The Functional Relation of Intercellular Substances in the Body to Certain Structures in the Egg Cell and Unicellular Organisms. By MONTROSE T. BURROWS, M. D.
Studies on the Growth of Cells *in vitro*. The Cultivation of Bladder and Prostate Tumors Outside the Body. By MONTROSE T. BURROWS, M. D., J. EDWARD BURNS, M. D., and YOSHIO SUZUKI, M. D.
The Study of a Small Outbreak of Poliomyelitis in an Apartment House, Occurring in the Course of an Epidemic in a Large City. By MONTROSE T. BURROWS, M. D., and EDWARDS A. PARK, M. D.
Papilloma of the Larynx. Report of a Case Treated with Radium with Resultant Chronic Diffuse Thyroiditis. By WILLIAM C. DUFFY, M. D.
Analysis of Autopsy Records.
Autopsy Statistics.
(a) Bay View.
(b) Johns Hopkins Hospital.
Report of the Photographic Department.
General Improvements.
Donations.

The set of eighteen volumes will be sold, bound in cloth, for $100.00 net. Volume II will not be sold separately. Volumes I, III, IV, V, VI, VII, VIII, X, XI, XII, XIII, XIV, XV, XVI, XVII and XVIII will be sold for $5.00, net, bound in paper, and $5.50, net, bound in cloth. Volume IX will be sold for $10.00 net.

Orders should be addressed to THE JOHNS HOPKINS PRESS, Baltimore, Md.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $3.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PPESS, BALTIMORE; single copies will be sent by mail for fifty cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.